Confidence intervals and point estimates for adaptive group sequential trials

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Outline

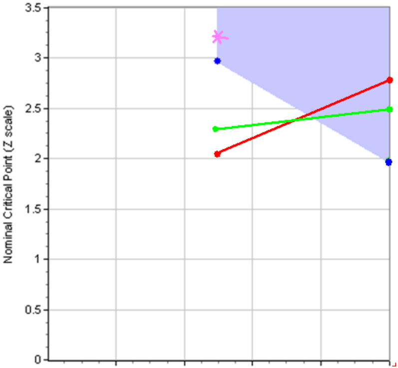
- Inference and ordering of sample space for classical group sequential design by Tsiatis, Rosner and Mehta (1984)
- Inference and ordering of sample space for adaptive group sequential design
- Application to the example
- Simulation results
- Conclusions

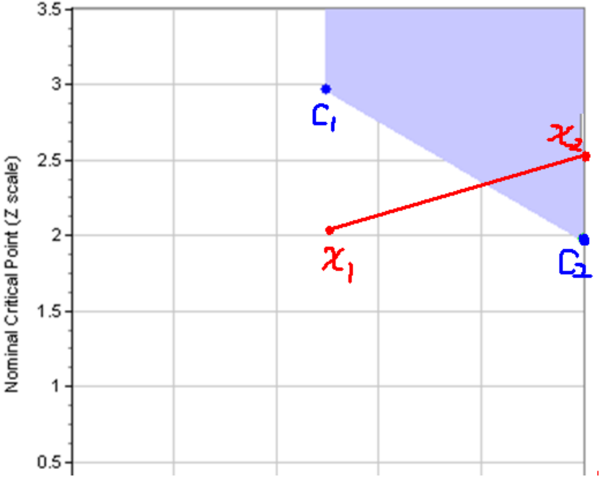
Review Inference Methods for Adaptive Group Sequential Design

- Repeated confidence interval (RCI) and repeated p value (RPV)
  - Classical group sequential design: Jennison and Turnbull (2000, Chapter 9) for classical group sequential designs
  - Adaptive setting: Lehmacher and Wassmer (1999) and more generally in Mehta, Bauer, Posch and Brannath (2007)
  - Only valid for adaptive changes in the sample size. They are not applicable if additional adaptive changes are made to the initial design, such as data dependent changes to the number and spacing of the interim looks, or changes to the error spending function.
  - Too conservative
- Stagewise adjusted confidence interval and p value (SWACI)
  - Classical group sequential design: Tsiatis, Rosner and Mehta (1984), exact two-sided confidence interval
  - Adaptive setting: Brannath, Mehta and Posch (2009) , exact one-sided confidence interval

Exact CI by Tsiatis, Rosner and Mehta (1984)

- Order sample space and define what is more extreme in classical group sequential
- Ordering between looks: the earlier the boundary is crossed, the more extreme the sample is
- Ordering within a look: the further the boundary is crossed, the more extreme the sample is





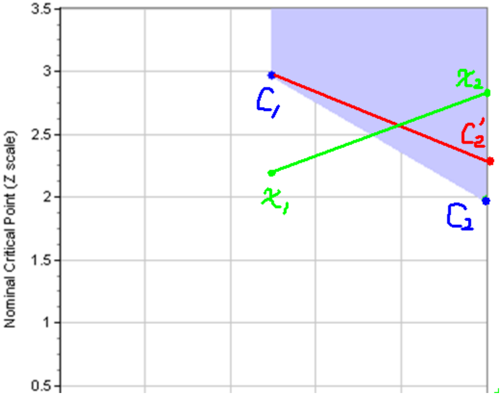
Nominal Critical Point (Z scale)
3.5
3
2.5
2
1.5
1
0.5

- The adjusted p value is the probability of all events which are more extreme than the observed one under the null hypothesis.
- The events which are more extreme than the oberserved one is given by $\{Z_1 > c_1 \text{ or } Z_2 > x_2\}$. Hence the adjusted p value is

$$p = P_0\left(Z_1 > c_1 \text{ or } Z_2 > x_2\right)$$

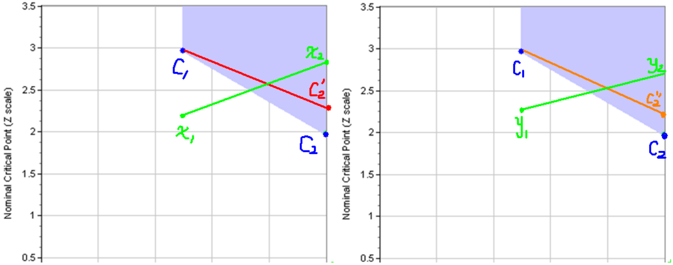
- Define $f\left(\delta\right) = P_\delta\left(Z_1 > c_1 \text{ or } Z_2 > x_2\right)$, $f\left(\delta\right)$ is an inceasing function of δ.
- The adjusted p value is nothing but $f\left(0\right)$.
- The median unbiased estimate $\hat{\delta}$ is the solution for $f\left(\hat{\delta}\right) = \frac{1}{2}$
- The lower confidence limit $\bar{\delta}_L$ satisfies the equation $f\left(\bar{\delta}_L\right) = \alpha$
- The upper confidence limit $\bar{\delta}_U$ satisfies the equation $f\left(\bar{\delta}_U\right) = 1 - \alpha$
- $\left(\bar{\delta}_L, \bar{\delta}_U\right)$ is a two-sided confidence interval with exact coverage probability of $1 - 2\alpha$.

Ordering of Sample Space in Adaptive Group Sequential Design—Mapping of Adaptive Design onto Initial Design



- What are the events which are more extreme than the observed one?
- Need to order the sample space of this adaptive design appropriately

Which one is more extreme?



- Boundary $c_2^{'}$ is adjusted to preserve the conditional type 1 error

$$P\left(Z_2^{'} > c_2^{'} \mid Z_1 = x_1\right) = P\left(Z_2 > c_2 \mid Z_1 = x_1\right)$$

- There exists a unique $x_{2,0} > c_2$ such that

$$P\left(Z_2^{'} > x_2 \mid Z_1 = x_1\right) = P\left(Z_2 > x_{2,0} \mid Z_1 = x_1\right)$$

- Similarly, $c_2^{''}$ satisfies

$$P\left(Z_2^{'} > c_2^{'} \mid Z_1 = x_1\right) = P\left(Z_2 > c_2 \mid Z_1 = x_1\right)$$

- There exists a unique $y_{2,0}$ such that

$$P\left(Z_2^{'} > y_2 \mid Z_1 = y_1\right) = P\left(Z_2 > y_{2,0} \mid Z_1 = y_1\right)$$

- $x_{2,0}$ is the backward image of x_2 and $y_{2,0}$ is the backward image of y_2.
- Order x_2 and y_2 according to their backward images $x_{2,0}$ and $y_{2,0}$ in the initial design.

- This ordering defines the events which are more extreme than the observed one $\{Z_1 > c_1 \text{ or } Z_2 > x_{2,0}\}$
- Define $f(\delta) = P_\delta(Z_1 > c_1 \text{ or } Z_2 > x_{2,0})$
- The adjusted p value is nothing but $f(0)$.
- The median unbiased estimate $\hat{\delta}$ is the solution for $f\left(\hat{\delta}\right) = \frac{1}{2}$
- The lower confidence limit $\bar{\delta}_L$ satisfies the equation

$$f\left(\bar{\delta}_L\right) = \alpha$$

- The upper confidence limit $\bar{\delta}_U$ satisfies the equation

$$f\left(\bar{\delta}_U\right) = 1 - \alpha$$

- $\left(\bar{\delta}_L, \bar{\delta}_U\right)$ is a two-sided confidence interval with exact coverage probability of $1 - 2\alpha$.

Apply to skin infection trial

Table: Two-look design; sample size adaptation at interim

δ	Exact confidence interval	
	SWACI(95% one-sided)	BSWACI(90% two-sided)
-0.1	-0.107647705	-0.107648849 ,0.260546684
0	-0.008255768	-0.008254051 ,0.360359192
0.15	0.113562012	0.11356163 ,0.50403595
0.3	0.163666534	0.163667679 ,0.692306519
0.5	0.363665771	0.363668442 ,0.892307281

Table: Two-look design; sample size adaptation at interim

δ	MUE		Adjusted p value	
	SWACI	BSWACI	SWACI	BSWACI
-0.1	0.076455688	0.076455116	0.207838797	0.207838797
0	0.176156616	0.176153898	0.030579995	0.030579995
0.15	0.31491394	0.314916134	0.001697488	0.001697488
0.3	0.427990723	0.427988052	0.000752883	0.000752883
0.5	0.627996826	0.627987862	1.60745E-06	1.60745E-06

Table: Exact confidence interval; 10000 simulations;3-look primary trial; adaptation at look 1; 3-look secondary trial

Design	True δ	One-sided 95% lower CL		Two-sided 90% CI
		BSWACI	SWACI	BSWACI
LD(OBF)-LD(PK)	-0.1	95	95.06	90.37
LD(OBF)-LD(PK)	0.0	94.92	95.059	89.768
LD(OBF)-LD(PK)	0.15	95.06	94.9	89.96
LD(OBF)-LD(PK)	0.3	94.74	94.61	89.23
LD(OBF)-LD(PK)	0.5	94.93	94.69	89.66

Table: Median unbiased estimates; 10000 simulations;3-look primary trial; adaptation at look 1; 3-look secondary trial

Design	True δ	SWACI(mean, median)	BSWACI(mean, median)
LD(OBF)-LD(PK)	-0.1	-0.1002, -0.0996	-0.1023, -0.1011
LD(OBF)-LD(PK)	0.0	-0.00099, -0.0003	-0.0017, 0.00049
LD(OBF)-LD(PK)	0.15	0.1533, 0.1457	0.1593, 0.1491
LD(OBF)-LD(PK)	0.3	0.2943, 0.2627	0.3199, 0.3016
LD(OBF)-LD(PK)	0.5	0.5053, 0.4976	0.5239, 0.5048

Table: Exact confidence Intervals; 10000 simulations; 3-look primary trial; adaptation at look 2; 3-look secondary trial

Design	True δ	One-sided 95% lower CL		Two-sided 90% CI
		BSWACI	SWACI	BSWACI
$\gamma(-4)$-$\gamma(-4)$	-0.1	0.9571	0.9493	0.9037
$\gamma(-4)$-$\gamma(-4)$	0.0	0.9505	0.9494	0.8993
$\gamma(-4)$-$\gamma(-4)$	0.15	0.9437	0.9522	0.8937
$\gamma(-4)$-$\gamma(-4)$	0.3	0.9517	0.9424	0.8965
$\gamma(-4)$-$\gamma(-4)$	0.5	0.9462	0.9465	0.9036

Table: Median unbiased estimates; 10000 simulations;3-look primary trial; adaptation at look 2; 3-look secondary trial

Design	True δ	SWACI(mean, median)	BSWACI(mean, median)
$\gamma(-4)$-$\gamma(-4)$	-0.1	-0.1002, -0.0978	-0.1037, -0.1019
$\gamma(-4)$-$\gamma(-4)$	0.0	-0.0040, 0.0005	-0.0015, -0.00009
$\gamma(-4)$-$\gamma(-4)$	0.15	0.1275, 0.0761	0.1627, 0.1500
$\gamma(-4)$-$\gamma(-4)$	0.3	0.2929, 0.3033	0.3276, 0.3102
$\gamma(-4)$-$\gamma(-4)$	0.5	0.5164, 0.4976	0.5223, 0.4985

Conclusions and Discussions

- The proposed method provides two-sided confidence intervals with exact coverage probability.
- If no adaptations are applied, the proposed method produces the same adjusted p values, median unbiased estimates, two-sided confidence intervals as Tsiatis, Rosner and Mehta (1984).
- When there is only one sample size modification, the one-sided confidence interval is identical to that of Brannath, Mehta and Posch (2009).
- This method is applicable to adaptive sequential designs with multiple adaptive changes.

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Thank you!