Unbiased estimation after modification of a group sequential design

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MCP 2007, 8-11 July 2007, Vienna

Group-sequential Designs

Group-sequential designs

- inspect the data at specified time points
- allow for early stopping with rejection or acceptance of the null hypothesis
    - ➡ early stopping for large effect size
    - ➡ fulfilling a power requirement for a range of effect sizes combined with small expected sample size
    - ➡ mostly smaller than the sample size of the corresponding fixed sample test

Ethical and economical reasons

➡ choosing group-sequential design

Model and Notations

Assumptions:

- K (interim) analyses at time points $t_1, \ldots, t_K = 1$, e.g. $t_i = \frac{n_i}{n_K}$ or information time fraction
- cumulative statistics S_{t_i} can be approximated by a Brownian Motion with drift δ

Then we have

➡ $S_{t_i} \sim N(t_i \delta, t_i)$

➡ $S_{t_i} - S_{t_{i-1}}$ and $S_{t_{i-1}}$ are independent

Design Modifications

Sometimes there are reasons to modify the ongoing trial

For example:

- **safety reasons**
  - need for more safety data than planned
- **external reasons**
  - a competing trial considered smaller effect sizes to be relevant
- **reasons from misspecified assumptions at the design stage**
  - misspecified nuisance parameter assumptions
  - misspecified range of effect sizes

The decision often depends on the observed data!

If the initial design was not planned as an adaptive one:

Can we change the original design without type I error inflation?

Design modifications

with control of the type I error level

(Cui et al., 1999; Müller & Schäfer, 2001, 2004)

General condition:

$$\mathbb{P}_{H_0}(\text{reject } H_0,\ \text{initial design}|\text{interim data})$$
$$\geq \mathbb{P}_{H_0}(\text{reject } H_0,\ \text{new design}|\text{interim data})$$

These Probabilities are called

Conditional Rejection Probabilities (CRP)

Modification in our model:

- can be easily calculated using the independency of the increments
  - ➡ results in a conditional type I error rate α^* for the remaining part of the trial
  - ➡ the new design has to have a type I error level of α^*

Types of Design Modifications

required in group-sequential design:

Data dependent change of

- **maximum sample size**
  - ➡ change of sample size between two consecutive analysis
- **number of stages**
  - ➡ insert or remove interim analyses
- α**-spending**
  - ➡ change the amount of the type I error spent at the interim analyses
- and their combinations

Mean unbiased estimator

for the drift parameter δ

- **Mean unbiased estimator from Rao-Blackwell**:
  If the trial stops at time point t_i

$$\hat{\delta}(s, t_i) = \mathbb{E}\{\frac{S_{t_1}}{t_1} | S_{t_i} = s\}$$

- can be computed recursively (Liu & Hall, 1999) quite similar to the "densities" in group-sequential designs

Properties

- does not depend on the design of the remaining part of the trial

➡ can be determined after data independent

  - stopping of the trial
  - adjustment of the stopping regions
  - modifications of time points of the interim analyses

- is the unique one, which has this property and depends on the sufficient statistics

But is biased if the design modifications depend on the interim data

Examples:

- data dependent

  - unplanned stopping of the trial
  - modification of the α-spending

Adapting the mean unbiased estimator

after modification of the design

Condition similar to the CRP-condition:

- **General:**

$$\mathbb{E}_\delta\{\text{ initial estimator } | \text{ interim data }\}$$
$$= \mathbb{E}_\delta\{\text{ new estimator } | \text{ interim data }\}$$

Adapting the unbiased estimator

in the fixed sample case

- **unbiased estimator at the original final analysis:** $\frac{S_{t_1}}{t_1}$
- **unplanned interim analysis at t_I:**

$$\mathbb{E}_\delta\{\frac{S_{t_1}}{t_1}|S_{t_I} = s\} = \frac{1}{t_1}\left(s + \mathbb{E}_\delta\{S_{t_1} - S_{t_I}\}\right) = \frac{1}{t_1}[s + (t_1 - t_I)\,\delta]$$

- **new final analysis at $\tilde{t}_1$:**
  Since $\mathbb{E}_\delta\{S_{\tilde{t}_1} - S_{t_I}\} = (\tilde{t}_1 - t_I)\,\delta$ the new estimator is

$$\frac{1}{t_1}[s + \frac{t_1 - t_I}{\tilde{t}_1 - t_I}\,(S_{\tilde{t}_1} - S_{t_I})]$$

Extension of a two-stage design

- initially planned: 2-stages, analyses at t_1 and t_2
- at the interim analysis (t_1): decision to extend the information time
- new final analysis at $\tilde{t}_2 > t_2$
- new estimator at the final analysis has to satisfy

$$\mathbb{E}_\delta\{\hat{\delta}(s + S_{t_2} - S_{t_1}, t_2)\} = \mathbb{E}_\delta\{\hat{\hat{\delta}}_s(S_{\tilde{t}_2} - S_{t_1}, \tilde{t}_2)\}$$

➡ Similar arguments as in Liu & Hall (1999) gives

$$\hat{\hat{\delta}}_s(x, \tilde{t}_2) = \frac{1}{\varphi_{\tilde{t}_2 - t_1}(x)} \int_{-\infty}^{\infty} \hat{\delta}(s + y, t_2)\varphi_{t_2 - t_1}(y)\varphi_{\tilde{t}_2 - t_2}(x - y)dy$$

Extension: example

- planned: analyses at $t_1 = 0.5, t_2 = 1$, $\alpha = 0.05$,$\alpha_1 = 0.02$, interim analysis $\longrightarrow$ final analysis at $\tilde{t}_2 = 1.2$

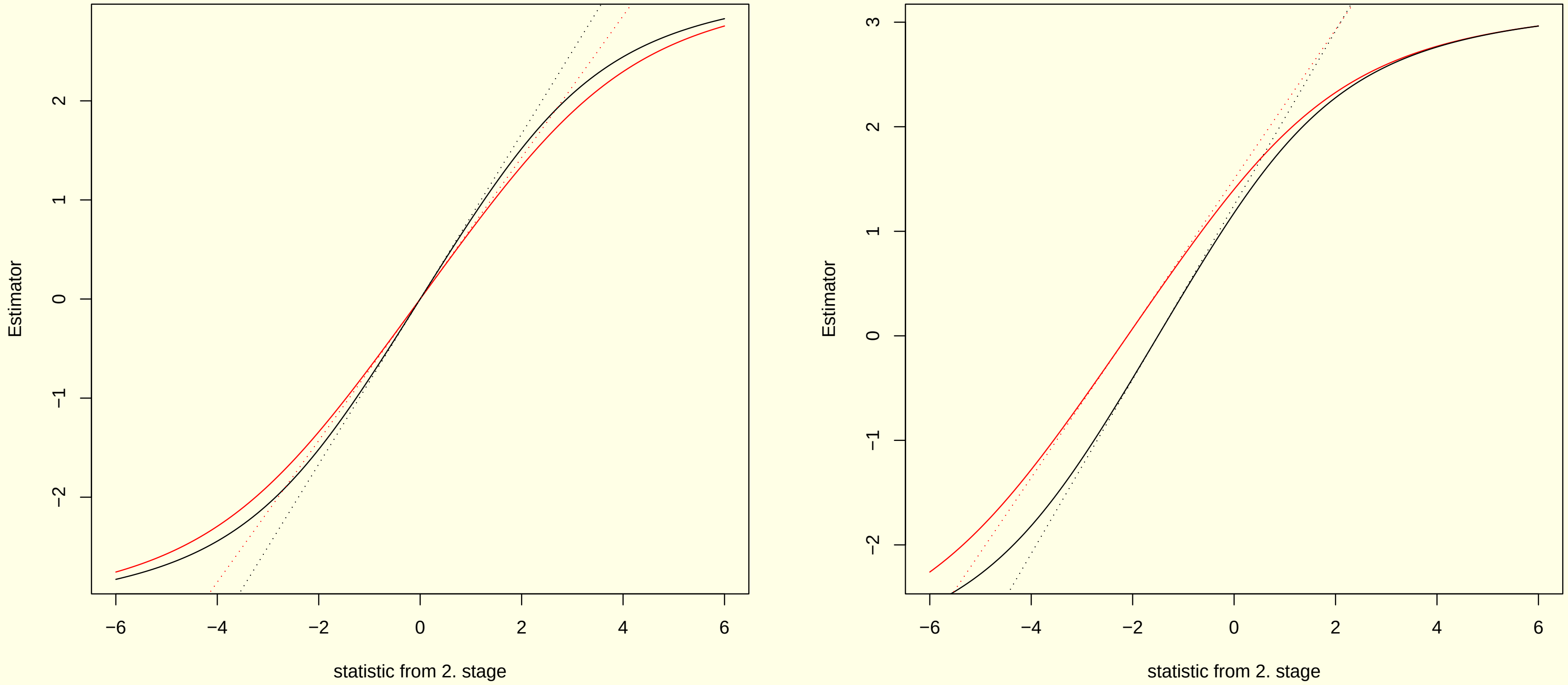

Figure 1: *fixed (dashed) and group-sequential estimator after extension of the information time (red lines) and for an initial design with $t_2 = 1.2$ and $s = 0$ (left) and $s = 1.5$*

Shortening of a two-stage design

- at the interim analysis decision to reduce information time ($\tilde{t}_2 < t_2$)
- ➡ new estimator at the final analysis is given by an integral equation

$$\hat{\delta}(s+y, t_2) = \frac{1}{\varphi_{t_2-t_1}(x)} \int_{-\infty}^{\infty} \hat{\tilde{\delta}}_s(y, \tilde{t}_2) \varphi_{\tilde{t}_2-t_1}(y) \varphi_{t_2-\tilde{t}_2}(x-y) dy$$

- ➡ can be computed numerical by discrete fourier transform

Shortening: example

- interim analysis $\longrightarrow$ final analysis at $\tilde{t}_2 = 0.8$

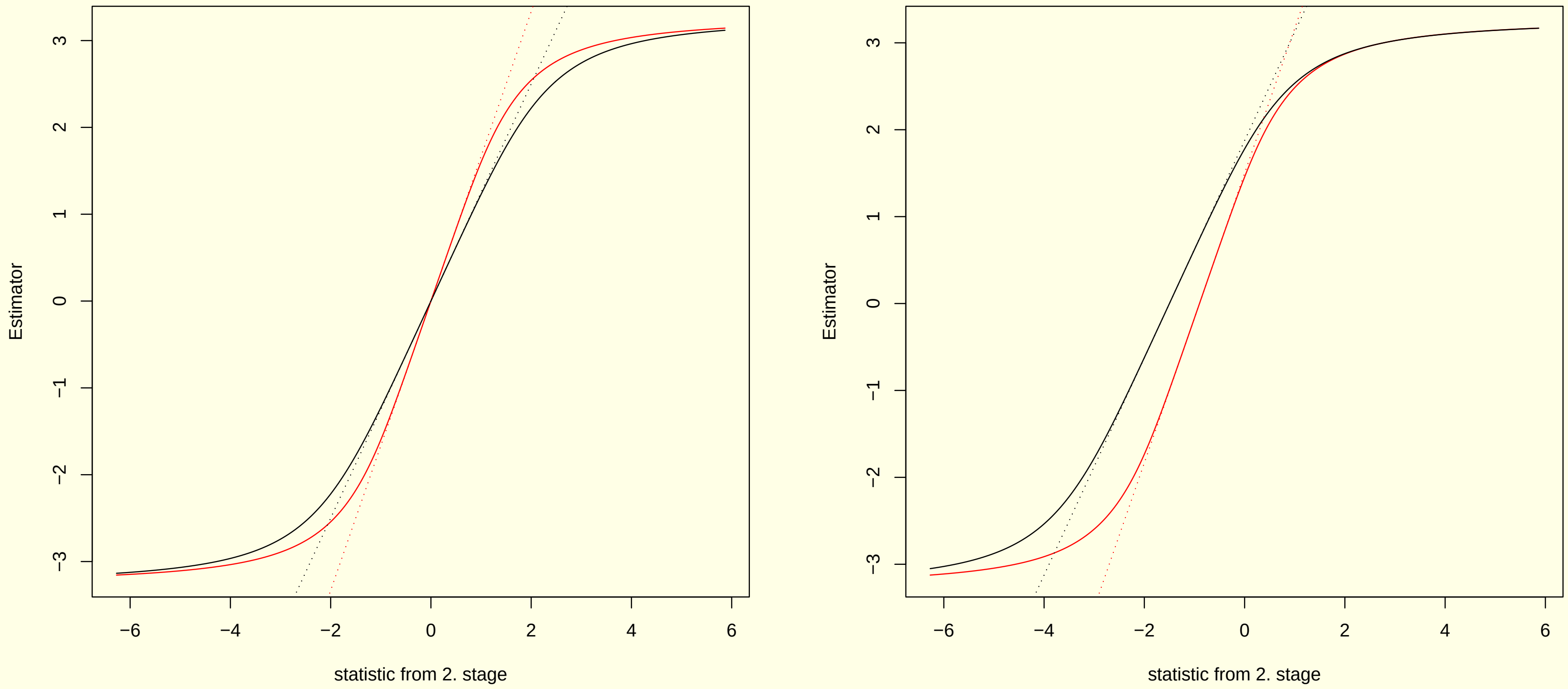

Figure 2: *fixed (dashed) and group-sequential estimator after shortening of the information time (red lines) and for an initial design with* $t_2 = 0.8$ *and* $s = 0$ *(left) and* $s = 1.5$

Reduction of the stage number

At an interim analysis it is decided to

- leave out further interim analyses
- to do only the final analysis at the planned time point t_K

Adaptation of the estimator:

- for each planned interim analyses, extend the estimator to the final analysis
  - ➡ *quite similar to the extension of a two stage design, only the integration regions and the densities have to modified slightly*
- the new estimator is the sum of all extended estimators

General modifications

The estimator can be obtained in 3 steps
Calculate the estimator for a group-sequential design

1. which has only one analysis at the initially planned final analysis (t_K)

   ➡ *last slide*

2. with one analysis at the time point of the first interim analysis of the modified design

   ➡ *shortening/ extension of a* 2*-stage design*

3. with analyses at the time points of the new design

   ➡ *recursive, similar as in Liu & Hall (1999)*

Conclusion

- the unbiased estimator
  - does not depend on the design of the remaining part of the trial
  - ➡ allows only for data independent modifications
- in the case of data dependent modifications
  - the estimator needs to be modified to maintain unbiasedness
  - the modified estimator can be calculated for all types of design modifications by
    - integration
    - solving integral equations
    - both of them
  - these computations might be complex

References

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