Estimation in Flexible Adaptive Designs

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Review of Flexible Two Stage Tests

Flexible designs

Flexible designs allow for mid-trial design modifications based on all internal and external information gathered at interim analyses without compromising the type I error rate.
For a control of the type I error rate, the design modifications need **not** be specified in advance.

Examples for mid-trial design modifications:

Adaptation of the sample sizes, dropping (or adding) study doses, adapting the number of interim analyses, decision boundaries, test statistics, the endpoints, the study goal (non-inferiority and superiority), the multiple testing strategy, ...

Pre-specified Adaptivity versus Flexibility

Pre-specified adaptivity =

adapting design parameters according to a pre-specified adaptation rule

Aims: Increasing efficiency by optimizing specific cost functions.

Examples: Group sequential trials, play-the-winner allocation rules, . . .

Flexibility ("unscheduled" adaptivity) =

adapting design parameters without a (complete) specification of the adaptation rule

Flexibility

Aims of flexibility:

- Dealing with the unexpected.
- Dealing with the expected unpredictability of clinical trials.
- Improving the “quality” of the decision process as a whole in an environment where the parameter assumptions and also the *weighting of gains and costs are unclear* a priori and can change in the course of the trial.

Flexible Two Stage Tests

Step-wise procedure

Consist of two sequential stages:
Stage 1 (e.g. Phase II part) and *Stage 2* (e.g. Phase III part)

Stage 1 and Stage 2 data are from two independent cohorts.

Adaptivity

The design of Stage 2 (sample sizes, statistical test, . . .) can be chosen based on the data of Stage 1 as well as any other internal or external information.

Flexibility

For a control of the type I error rate, one need not pre-specify how the Stage 1 data determine the design of Stage 2.

Flexible two stage combination tests

Notation: p and q the p-values from stage 1 and 2 for

$$H_0 : \theta \leq 0 \quad \text{versus} \quad H_1 : \theta > 0$$

p and q are independent under H_0.

Two stage combination test: Prefix a monotone combination function $C(p, q)$ and rejection bounds c and α_1.

$$\text{We reject } H_0 \text{ if} \quad \begin{array}{lrl} \text{either} & p \leq \alpha_1 & \text{(stage 1)} \\ \text{or} & C(p, q) \leq c & \text{(stage 2)} \end{array}$$

Level condition: We must prefix α_1, $C(p, q)$ and c such that

$$P_0(\{p \leq \alpha_1\} \cup \{C(p, q) \leq c\}) = \alpha$$

Examples for combination functions

- Fisher's product test:

$$C(p,q) = p \cdot q$$

- Inverse normal method:

$$C(p,q) = w_1\,\Phi^{-1}(p) + w_2\,\Phi^{-1}(q), \quad w_1^2 + w_2^2 = 1$$

Gives a two stage GSD with information times $t_1 \leq t_2$ if $w_1/w_2 = \sqrt{t_1/(t_2 - t_1)}$ and no adaptations are done.

Estimation

"Corresponding methods to estimate the size of the treatment effect and to provide confidence intervals with pre-specified coverage probability are additional requirements."

Reflection paper on flexible designs (Draft), EMEA 2006

Bias of conventional estimates

- Unblinded sample size adaptations may lead to (mean) biased estimates and invalid confidence intervals.
- Sample size adaptation rule unkown
  $\rightarrow$ bias and coverage probabilities **unknown.**

Confidence intervals for flexible designs

- Duality between confidence sets and significance tests:

  confidence set $=$ set of values where significance test accepts

- Flexible confidence interval:

  Use flexible tests at level α for all parameter values

- Flexible confidence intervals have coverage probability $\geq 1 - \alpha$ independently of the adaptation rule.

- Overall p-values can be constructed in a similar way.

Confidence intervals for flexible designs accounting for stopping rules

Two possible approaches:

- *Repeated confidence interval approach:*
  is very simple; flexibility also with regard to stopping rule; inevitable price is strict conservatism.

- *Exact confidence interval via stage wise ordering:*
  is more complicated; no flexibility with regard to stopping rule; exact coverage probability.

  Exact confidence interval at level 0.5 gives median unbiased point estimate which lies in the interior of the exact 95%-confidence interval.

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Chapter 2: Repeated Confidence Intervals

(Lehmacher & Wassmer, 1999; Brannath et al. 2002, Lawrence & Hung, 2003; Proschan et al., 2003)

Repeated confidence intervals

Duality between hypothesis tests and confidence sets:

p_Δ stage 1 and q_Δ stage 2 p-values for $H_{0,\Delta} : \theta \leq \Delta$.

p_Δ and q_Δ independent under $H_{0,\Delta}$ and increasing in Δ.

Two stage combination test for $H_{0,\Delta}$: Use for all Δ the same combination test.

We reject $H_{0,\Delta}$ if either $p_\Delta \leq \alpha_1$ (stage 1)

or $C(p_\Delta, q_\Delta) \leq c$ (stage 2)

Remark: The rule "$p_\Delta \leq \alpha_1$" should *not* be understood as a *stopping rule*, but as *rejection rule* which we apply at stage 1.

Lower repeated confidence bounds

Stage 1: Solve the equation $p_\Delta = \alpha_1 \quad \rightarrow \quad \delta_1$ such that

$$p_\Delta \leq \alpha_1 \quad \Longleftrightarrow \quad \Delta \leq \delta_1$$

$\rightarrow \quad (\delta_1, \infty)$ one-sided confidence interval at first stage.

Stage 2: Solve $C(p_\Delta, q_\Delta) = c \quad \rightarrow \quad \delta_2$ such that

$$C(p_\Delta, q_\Delta) \leq c \quad \Longleftrightarrow \quad \Delta \leq \delta_2$$

$\rightarrow \quad (\delta_2, \infty)$ one-sided confidence interval at second stage.

Example I

Primary efficacy end point: Infarct size measured by the cumulative release of α-HDBH within 72 hours after administration of the drug (area under the curve, AUC).

θ the mean α-HDBH AUC difference between control c and treatment t, $H_0 : \theta \leq 0$ vs. $H_1 : \theta > 0$

Inverse normal combination test:

$$C(p, q) = \sqrt{0.5} \cdot \Phi^{-1}(p) + \sqrt{0.5} \cdot \Phi^{-1}(q)$$

O'Brien and Flemming at one sided level $\alpha = 0.025$

$\rightarrow \alpha_1 = 0.0026$, $c = 0.024$.

Example I (cont.)

Stage 1: sample sizes: $n_{1c} = 88$, $n_{1t} = 91$,
standard deviation: $\hat{\sigma}_{1c} = 26.0$, $\hat{\sigma}_{1t} = 22.5$
treatment difference: $\hat{\theta}_1 = 4.0$, $\sigma_{\hat{\theta}_1} = 3.64$

p_Δ according to t-test for $H_0 : \theta = \Delta$.

Solving $p_\Delta = 0.0026 \quad \longrightarrow \quad$ classical CI at level 0.0026

$$\delta_1 = \hat{\theta}_1 - t_{\nu,0.9974} \cdot \sigma_{\hat{\theta}_1} = -6.3$$

First stage confidence interval is $(-6.3, \infty)$

Example I (cont.)

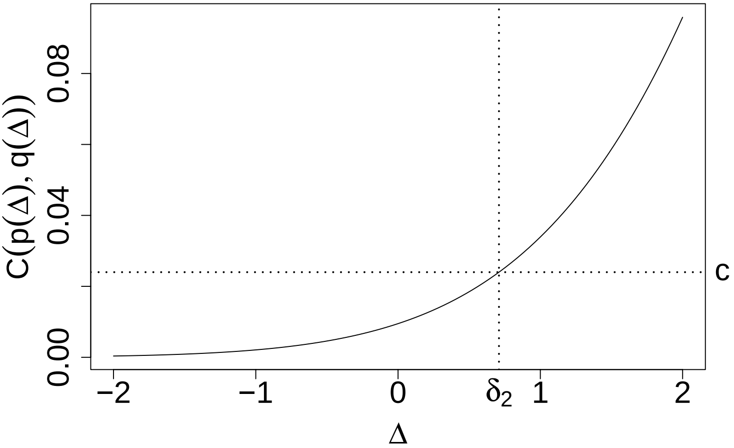
Stage 2: sample sizes $n_{2c} = 322$, $n_{2t} = 321$,
standard deviations: $\hat{\sigma}_{2c} = 26.1$, $\hat{\sigma}_{2t} = 28.5$,
treatment difference: $\hat{\theta}_2 = 4.8$, $\sigma_{\hat{\theta}_2} = 2.16$

q_Δ according to t-test for $H_0 : \theta = \Delta$ from second stage data.

Solving $C(p_\Delta, q_\Delta) = 0.024$ numerically $\longrightarrow$ $\delta_2 = 0.71$

Second stage confidence interval is $(0.71, \infty)$

Example I (cont.): Determination of δ_2



Properties of repeated confidence bounds

- One need not pre-specify the adaptation and stopping rule to keep the nominal coverage probability.
- Price for the flexibility with regard to stopping rule is strict conservatism: we must control the level for the worst case rule, also when actually not following this rule.
- H_0 is rejected with the combination test iff $\delta_L > 0$.
- The first stage bound δ_1 is the classical confidence bound at level α_1.

Normal approximations and inverse normal method (Lehmacher and Wassmer, 1999)

If the stage wise estimates $\hat{\theta}_i$ ($i = 1, 2$) for the treatment effect are asymptotically independent and normal with mean treatment effect Δ and variance $\sigma^2_{\hat{\theta}_i} = I_1^{-1}$, then

$$p(\Delta) = 1 - \Phi(\sqrt{I_1} \cdot (\hat{\theta}_1 - \Delta)) \quad \text{and} \quad q(\Delta) = 1 - \Phi(\sqrt{I_2} \cdot (\hat{\theta}_2 - \Delta))$$

are approximate independent p-values for $H_{0,\Delta} : \theta \leq \Delta$.

Inverse normal combination function

$$\delta_2 = \widehat{\theta}_w - \frac{\Phi^{-1}(1-c)}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_1}}, \quad \widehat{\theta}_w = \frac{w_1 \cdot \sqrt{I_1} \cdot \hat{\theta}_1 + w_2 \cdot \sqrt{I_2} \cdot \hat{\theta}_2}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_2}}$$

Example I with normal approximation

Stage 1: $\hat{\theta}_1 = 4.0, \quad I_1 = 0.076$

$$\delta_1 = 4.0 - \Phi^{-1}(0.9974) \cdot \sqrt{I_1} = -6.2 \quad \text{(before } -6.3\text{)}$$

Stage 2: $\hat{\theta}_2 = 4.8, \quad I_2 = 0.215, \quad w_1 = w_2 = \sqrt{0.5}$

$$\widehat{\theta}_w = \frac{\sqrt{I_1} \cdot \hat{\theta}_1 + \sqrt{I_2} \cdot \hat{\theta}_2}{\sqrt{I_1} + \sqrt{I_2}} = 4.5$$

$$\delta_1 = 4.5 - \frac{\Phi^{-1}(1 - 0.024)}{(\sqrt{I_1} + \sqrt{I_2})\sqrt{0.5}} = 0.70 \quad \text{(before } 0.71\text{)}$$

Extensions

- Repeated confidence intervals can be extended to multistage flexible designs, and can be computed even after adapting the number of interim looks

  (Lehmacher and Wassmer, 1999; Brannath et al., 2002)

- One can incorporate a futility boundary into the dual combination tests. However, one must carefully account for the futility bound in the determination of δ_2:

  One must accept all Δ for which stage 1 p-value p_Δ falls into stage 1 acceptance region even if the second stage data suggest rejection of $H_{0,\Delta}$.

Extensions

- We could use different α_1 and c for different Δ, however, one must be careful in our choice in α_1 and c in order to get nested dual rejection regions. (BRANNATH ET AL. 2003)
- Exact confidence intervals and median unbiased point estimates are available via the stage wise ordering. (BRANNATH ET AL. 2002)
- Confidence intervals and point estimates for adaptive GSD's following the principle of Müller and Schäfer have been derived only recently. (METHA, BRANNATH, POSCH AND BAUER 2006; SUBMITTED)

Two-sided tests and two-sided confidence intervals at level 2α

- One should not perform combination tests with two-sided p-values for $H_{0,\Delta} : \theta = \Delta$:

  Interpretation problem if the first and the second stage estimates point in conflictive directions.
- *Solution:* Intersection of two one-sided combination tests and corresponding repeated confidence intervals (one lower and one upper) each at level α.

Two-sided confidence intervals at level 2α

- At the first stage we get the classical two-sided interval at level $2\alpha_1$.
- With the normal approximation and normal inverse method we get at the second stage the interval

$$\left(\widehat{\theta}_w - \frac{\Phi^{-1}(1-c)}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_2}}, \widehat{\theta}_w + \frac{\Phi^{-1}(1-c)}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_2}}\right)$$

with

$$\widehat{\theta}_w = \frac{w_1 \cdot \sqrt{I_1} \cdot \hat{\theta}_1 + w_2 \cdot \sqrt{I_2} \cdot \hat{\theta}_2}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_2}}$$

Confidence intervals for the conditional error function approach

Conditional error function approach: Prefix a decreasing conditional error function $A(x)$ and first stage rejection level α_1.

$$\text{Reject } H_0 \text{ if } \quad p \le \alpha_1 \text{ (stage 1)} \quad \text{or} \quad q \le A(p) \text{ (stage 2)}.$$

Equivalent combination test (POSCH & BAUER 1999, WASSMER 1999):

$$e.g. \qquad \alpha_1, \quad C(p,q) = q - A(p), \quad \text{and} \quad c = 0$$

$\rightarrow$ One can use the same estimation methods as for combination tests

Chapter 3: Point Estimation

Maximum likelihood estimate (MLE)

Assuming normal data and balanced treatment groups the MLE can be written as

$$\hat{\theta}_{mle} = \frac{I_1}{I_1 + I_2} \cdot \hat{\theta}_1 + \frac{I_2}{I_1 + I_2} \cdot \hat{\theta}_2$$

(for small effect sizes approximatively also in other cases)

Mean Bias: $E_\Delta(\hat{\theta}_{mle} - \Delta) = Cov_\Delta(\frac{I_1}{I_1+I_2}, \hat{\theta}_1)$ (Liu et al. 2002)

One can show that always: $|E_\Delta(\hat{\theta}_{mle} - \Delta)| \leq 0.4 \cdot \sigma/\sqrt{n_1}$

Variance also depends on (unknown) adaptation/selection rule

Maximum likelihood estimate (MLE)

Mean bias of MLE for typical examples (qualitatively):

- *Stopping with early rejection:* the larger the effect size the smaller the sample size $\rightarrow$ positive mean bias.
- *Stopping for futility:* the smaller the effect size the smaller the sample size $\rightarrow$ negative mean bias.
- *Conditional or predictive power control:* the smaller the effect size the larger the sample size $\rightarrow$ positive mean bias.
- *Selecting promising treatments:* the larger the effect size the larger the sample size $\rightarrow$ negative mean bias.

Weighted maximum likelihood estimate

Center of a two sided repeated confidence interval:

$$\widehat{\theta}_w = \frac{w_1 \cdot \sqrt{I_1} \cdot \hat{\theta}_1 + w_2 \cdot \sqrt{I_2} \cdot \hat{\theta}_2}{w_1 \cdot \sqrt{I_1} + w_2 \cdot \sqrt{I_2}}$$

where $w_1, w_2 \geq 0$, $w_1^2 + w_2^2 = 1$ are the pre-specified weights.

Properties:

- If recruitment is stopped at stage 1 then $\widehat{\theta}_w = \hat{\theta}_1$.
- If recruitment is never stopped at the interim analysis, then $\hat{\theta}_w$ is *median unbiased*, i.e., $\hat{\theta}_w$ has median Δ.
- Median of $\hat{\theta}_w$ close to Δ also if recruitment can be stopped at interim analysis.

Cases for which the estimates are similar

The two estimates are equal or differ only slightly if

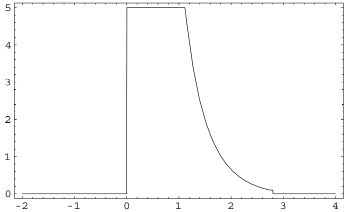
- recruitment is stopped at the interim analysis;
- recruitment is **not** stopped at the interim analysis, and
    - the first and second stage estimates are similar, $\hat{\theta}_1 \approx \hat{\theta}_2$;

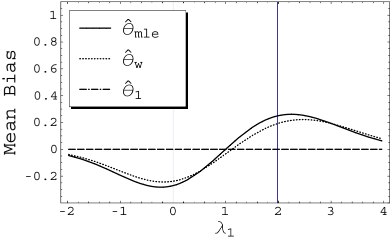
  or
    - the sample sizes are (almost) as pre-planned: $\sqrt{I_1/I_2} \approx w_1/w_2 = \sqrt{t_1/(t_2 - t_1)}$

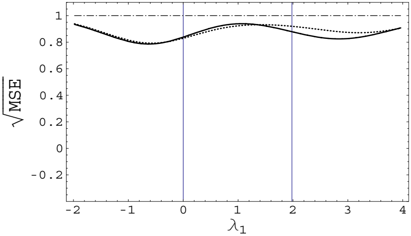
Numerical example

80% - Predictive power rule,
truncated $0.1 \cdot I_1 \leq I_2 \leq 5 \cdot I_1$.

$\widehat{\theta}_w$ with $w_1^2 = 0.5$
$\hat{\theta}_1$ first stage mean diffenrence
horizontal axis: $\lambda_1 = \sqrt{I_1} \cdot \theta$







Remarks on Seamless Phase II/III designs

- Start with a number of treatments (doses) and *select treatments* and reassess sample sizes at an adaptive interim analysis.
- Selection rule is typically **not** fully pre-specified.
- Flexible closed tests provide strong FWER control.

- Repeated confidence interval approach provides univariate confidence intervals (no multiplicity adjustment).
- Simultaneous confidence intervals which are consistent with the (multiple) test result may **not** be available.
- Mean or median unbiased estimates are currently **not** available.
- Selection bias can be an additional issue (ongoing research and discussion).

Summary

- Univariate confidence intervals are, in general, available for flexible adaptive designs.
- Using the normal approximation of stage wise estimates and the inverse normal combination function, we get explicit (and intuitive) formula for the confidence bounds.
- Maximum likelihood estimate is biased, however, seems to perform well in terms of the mean square error.
- The *weighted maximum likelihood estimate* is, in general, less biased and median unbiased in the case of an administrative interim look.
- With a stopping rule a median unbiased estimate can be obtained via the stage wise ordering.

Selected literature

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