Group-Sequential and Two-Stage Designs

Helmut Schütz
Nothing is ‘carved in stone’.

- Never assume perfectly matching products.
  - Generally a $\Delta$ of not better than 5% should be assumed (0.950 – 1.053).
  - For HVD(P)s do not assume a $\Delta$ of <10% (0.900 – 1.111).

- Do not use the CV but one of its confidence limits.
  - Suggested $\alpha$ 0.2 (here: the producer's risk).
  - For ABE the upper CL.
  - For reference-scaling (generally) the lower CL.

- Better alternatives.
  - Group-Sequential Designs
    Fixed total sample size, interim analysis for early stopping.
  - (Adaptive) Sequential Two-Stage Designs
    Fixed stage 1 sample size, re-estimation of the total sample size in the interim analysis.
Remedies?

Group-Sequential Designs

- Fixed total sample size \((N)\) and – in BE – one interim analysis.
  - Requires two assumptions. One ‘worst case’ \(CV\) for the total sample size and a ‘realistic’ \(CV\) for the interim.
  - All published methods were derived for superiority testing, parallel groups, normal distributed data with known variance, and interim at \(N/2\).
  - That’s not what we have in BE: equivalence (generally in a crossover), lognormal data with unknown variance. Furthermore, due to drop-outs, the interim might not be exactly at \(N/2\) (might inflate the Type I Error).
  - Asymmetric split of \(\alpha\) is possible, i.e., a small \(\alpha\) in the interim and a large one in the final analysis.
    Examples: Haybittle/Peto \((\alpha_1 0.001, \alpha_2 0.049)\), O’Brien/Fleming \((\alpha_1 0.005, \alpha_2 0.048)\), Zheng et al. \((\alpha_1 0.01, \alpha_2 0.04)\).
    May require \(\alpha\)-spending functions (Lan/DeMets, Jennison/Turnbull) in order to control the Type I Error.
Remedies?

(Adaptive) Sequential Two-Stage Designs

- Fixed stage 1 sample size \( (n_1) \), sample size re-estimation in the interim.
  - Generally a fixed GMR is assumed.
  - Fully adaptive methods (i.e., taking also the PE of stage 1 into account) are problematic. May deteriorate power and require a futility criterion. Simulations mandatory.
  - Two ‘Types’ (Schütz 2015)
    1. The same adjusted \( \alpha \) is applied in both stages (regardless whether a study stops in the first stage or proceeds to the second stage).
    2. An unadjusted \( \alpha \) may be used in the first stage, dependent on interim power.
Group-Sequential Designs

Long and accepted tradition in clinical research (phase III)

  - Developed for superiority testing, parallel groups, normal distributed data with known variance, and interim at $N/2$.
  - Asymmetric split of $\alpha$ is possible, i.e.,
    - a small $\alpha$ in the interim (i.e., stopping for futility) and
    - a large one in the final analysis (i.e., only small sample size penalty).
  - Examples: Haybittle/Peto ($\alpha_1 0.001$, $\alpha_2 0.049$), O’Brien/Fleming ($\alpha_1 0.005$, $\alpha_2 0.048$).
  - Not developed for crossover designs and sample size re-estimation (fixed $n_1$ and variable $N$): Lower $\alpha_2$ or $\alpha$-spending functions (Lan/DeMets, Jennison/Turnbull) are needed in order to control the Type I Error.
  - Zheng et al. (2015) for BE in crossovers ($\alpha_1 0.01$, $\alpha_2 0.04$) controls the TIE.
Excursion

Type I Error and power

- Fixed sample $2 \times 2 \times 2$ design ($\alpha = 0.05$). $GMR = 0.95$, $CV = 10 - 80\%$, $n = 12 - 72$
Group-Sequential Designs

Type I Error

Haybittle/Peto
\( \alpha_1 0.001, \alpha_2 0.049 \)

O’Brien/Fleming
\( \alpha_1 0.005, \alpha_2 0.048 \)

Zheng et al.
\( \alpha_1 0.01, \alpha_2 0.04 \)

Maximum 0.05849
\( \alpha_2 0.0413 \) needed to control the TIE

Maximum 0.05700
\( \alpha_2 0.0415 \) needed to control the TIE

Maximum 0.04878
Review of Guidelines

• Australia (2004), Canada (Draft 2009)
  – Application of Bonferroni’s correction ($\alpha_{adj} 0.025$).
  – Theoretical TIE $\leq 0.0494$.
  – For CVs and samples sizes common in BE the TIE generally is $\leq 0.04$.

• Canada (2012)
  – Pocock’s $\alpha_{adj} 0.0294$.
  – $n_1$ based on ‘most likely variance’ + additional subjects in order to compensate for expected dropout-rate.
  – $N$ based on ‘worst-case scenario’.
  – If $n_1 \neq N/2$ relevant inflation of the TIE is possible! $\alpha$-spending functions can control the TIE (but are not mentioned in the guidance).
(Adaptive) Sequential Two-Stage Designs

Fixed stage 1 sample size \( (n_1) \), sample size re-estimation in the interim.

- Generally a fixed GMR is assumed.
- All published methods are valid only for a range of combinations of stage 1 sample sizes, CVs, GMRs, and desired power.
- Contrary to common believes no analytical proof of controlling the TIE exist. It is the responsibility of the sponsor to demonstrate (e.g., by simulations) that the consumer risk is preserved.
- Fully adaptive methods (i.e., taking also the PE of stage 1 into account) are problematic. May substantially deteriorate power and require a futility criterion. Simulations mandatory.
Type 1 and Type 2

**Interim power based on**

\[ \text{GMR}, \alpha_{adj}, \text{and observed CV} \]

**Total sample size** \( N \) **based on**

\[ \text{GMR, } \alpha_{adj}, \pi, \text{and observed CV} \]

**Stage 2 with** \( n_2 = N - n_1 \)

**100(1 - 2\alpha_{adj}) CI using pooled data of both stages** \( (\alpha_{adj}) \)

**Pass or fail**
Excursion

Type I Error and power

- Fixed sample $2 \times 2 \times 2$ design ($\alpha = 0.05$). \textit{GMR} 0.95, \textit{CV} 10 – 80%, \textit{n} 12 – 72
Excursion

Type I Error and power

- ‘Type 1’ TSD (Potvin Method B, $\alpha_{adj} 0.0294$). GMR 0.95, CV 10 – 80%, $n_1$ 12 – 72
(Adaptive) Sequential Two-Stage Designs

Methods by Potvin et al. (2008) first validated framework in the context of BE

- Supported by the ‘Product Quality Research Institute’ (FDA/CDER, Health Canada, USP, AAPS, PhRMA…).
- Inspired by conventional BE testing and Pocock’s $\alpha_{adj}$ 0.0294 for GSDs.
  - A fixed GMR is assumed (only the CV in the interim is taken into account for sample size re-estimation). GMR in the first publication was 0.95; later extended to 0.90 by other authors.
  - Target power 80% (later extended to 90%).
(Adaptive) Sequential Two-Stage Designs

Frameworks for crossover TSDs

- **Stage 1** sample sizes 12 – 60, no futility rules.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Method</th>
<th>GMR</th>
<th>Target power</th>
<th>CV&lt;sub&gt;w&lt;/sub&gt;</th>
<th>α&lt;sub&gt;adj&lt;/sub&gt;</th>
<th>TIE&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potvin et al. (2008)</td>
<td>1</td>
<td>B</td>
<td>0.95</td>
<td>80%</td>
<td>10 – 100%</td>
<td>0.0294</td>
<td>0.0485</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>C</td>
<td>0.95</td>
<td>80%</td>
<td>10 – 100%</td>
<td>0.0294</td>
<td>0.0510</td>
</tr>
<tr>
<td>Montague et al. (2012)</td>
<td>2</td>
<td>D</td>
<td>0.90</td>
<td></td>
<td></td>
<td>0.0280</td>
<td>0.0518</td>
</tr>
<tr>
<td>Fuglsang (2013)</td>
<td>1</td>
<td>B</td>
<td>0.95</td>
<td></td>
<td></td>
<td>0.0284</td>
<td>0.0501</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>C/D</td>
<td>0.95</td>
<td>90%</td>
<td>10 – 80%</td>
<td>0.0274</td>
<td>0.0503</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>C/D</td>
<td>0.90</td>
<td></td>
<td></td>
<td>0.0269</td>
<td>0.0501</td>
</tr>
</tbody>
</table>

- **Xu et al. (2015)**. GMR 0.95, target power 80%, futility for the (1–2α<sub>1</sub>) CI.

<table>
<thead>
<tr>
<th>Type</th>
<th>Method</th>
<th>CV&lt;sub&gt;w&lt;/sub&gt;</th>
<th>Futility region</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2&lt;/sub&gt;</th>
<th>TIE&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>0.9374 – 1.0667</td>
<td>10 – 30%</td>
<td>0.0249</td>
<td>0.0363</td>
<td>0.050</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>0.9492 – 1.0535</td>
<td>0.9492 – 1.0535</td>
<td>0.0248</td>
<td>0.0364</td>
<td>0.050</td>
</tr>
<tr>
<td>1</td>
<td>E</td>
<td>0.9305 – 1.0747</td>
<td>30 – 55%</td>
<td>0.0254</td>
<td>0.0357</td>
<td>0.050</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>0.9350 – 1.0695</td>
<td>0.9350 – 1.0695</td>
<td>0.0259</td>
<td>0.0349</td>
<td>0.050</td>
</tr>
</tbody>
</table>
(Adaptive) Sequential Two-Stage Designs

Review of Guidelines

- EMA (Jan 2010)
  - Acceptable.
  - $\alpha_{adj} = 0.0294 = 94.12\%$ CI in both stages given as an example (i.e., Potvin Method B preferred?)
  - ‘... there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company’s discretion.’
  - ‘... pre-specified ... adjusted significance levels to be used for each of the analyses.’
  - Remarks
    - The TIE must be preserved. Especially important if ‘exotic’ methods are applied.
    - Does the requirement of pre-specifying both alphas imply that $\alpha$-spending functions or adaptive methods (where $\alpha_2$ is based on the interim and/or the final sample size) are not acceptable?
    - TSDs are on the workplan of the EMA’s Biostatistics Working Party for 2017...
(Adaptive) Sequential Two-Stage Designs

Review of Guidelines

- **EMA Q&A Document Rev. 7 (Feb 2013)**
  - The model for the combined analysis is (all effects fixed):
    
    \[
    \text{stage} + \text{sequence} + \text{sequence(stage)} + \text{subject(sequence \times stage)} + \\
    \text{period(stage)} + \text{formulation}
    \]
  - At least two subjects in the second stage.
  - Remarks
    - *None* of the publications used `sequence(stage)`;
      no poolability criterion – combining is always allowed, even if a significant difference between stages is observed.
      Simulations performed by the BSWP or out of the blue?
    - Modification shown to be irrelevant (Karalis/Macheras 2014). Furthermore, no difference whether subjects are treated as a fixed or random term (unless PE >1.20). Requiring two subjects in the second stage is unnecessary.
      ```r
      library(Power2Stage)
      power.2stage(method="B", CV=0.2, n1=12, theta0=1.25)$pBE
      [1] 0.046262
      power.2stage(method="B", CV=0.2, n1=12, theta0=1.25, min.n2=2)$pBE
      [1] 0.046262
      ```
Review of Guidelines

- Health Canada (May 2012)
  - Potvin Method C recommended.
- FDA
- Russia (2013), Eurasian Economic Union (2016)
  - Acceptable; Potvin Method B preferred?
(Adaptive) Sequential Two-Stage Designs

Futility Rules

• Futility rules (for early stopping) do not inflate the TIE, but may deteriorate power.
  
  – Stopping criteria must be unambiguously stated in the protocol.
  – Simulations are mandatory in order to assess whether power is sufficient:
    Introduction of [...] futility rules may severely impact power in trials with sequential designs and under some circumstances such trials might be unethical.

  Fuglsang 2014

  […] before using any of the methods [...] , their operating characteristics should be evaluated for a range of values of \( n_1, CV \) and true ratio of means that are of interest, in order to decide if the Type I error rate is controlled, the power is adequate and the potential maximum total sample size is not too great.

  Jones/Kenward 2014

  – Simulations uncomplicated with current software.
    – Finding a suitable \( \alpha_{adj} \) and validating for TIE and power takes \( \sim 20 \) minutes with the R-package Power2Stage (open source).
(Adaptive) Sequential Two-Stage Designs

Dropouts and overrun studies

- ** Dropouts in the second stage
  - A smaller total sample size translates into a lower chance to show BE and hence, also a lower Type I Error.
  - Like in fixed sample designs the impact on power will be small.

- ** Including more than the re-estimated subjects in the second stage
  - Common practice in fixed sample designs ‘in order to compensate for loss in power based on the expected dropout-rate’.
  - If less dropouts occur in the second stage, the study is ‘overrun’. The chance to show BE increases and therefore, the TIE!
  - Methods exists in the literature (though for parallel designs, superiority testing only) to adjust $\alpha$ accordingly. Nothing published for equivalence yet.
  - Don’t go there.
(Adaptive) Sequential Two-Stage Designs

Cost Analysis

• Consider certain questions:
  – Is it possible to assume a best/worst-case scenario?
  – How large should the size of the first stage be?
  – How large is the expected average sample size in the second stage?
  – Which power can one expect in the first stage and the final analysis?
  – Will introduction of a futility criterion substantially decrease power?
  – Is there an unacceptable sample size penalty compared to a fixed sample design?
### (Adaptive) Sequential Two-Stage Designs

#### Cost Analysis

- **Example:**
  - Expected CV 20%, target power is 80% for a *GMR* of 0.95. Comparison of a ‘Type 1’ TSD with a fixed sample design (*n* 20, 83.5% power).

<table>
<thead>
<tr>
<th>$n_1$</th>
<th>$E[N]$</th>
<th>Studies stopped in stage 1 (%)</th>
<th>Studies failed in stage 1 (%)</th>
<th>Power in stage 1 (%)</th>
<th>Studies in stage 2 (%)</th>
<th>Final power (%)</th>
<th>Increase of costs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>20.6</td>
<td>43.6</td>
<td>2.3</td>
<td>41.3</td>
<td>56.4</td>
<td>84.2</td>
<td>+2.9</td>
</tr>
<tr>
<td>14</td>
<td>20.0</td>
<td>55.6</td>
<td>3.0</td>
<td>52.4</td>
<td>44.5</td>
<td>85.0</td>
<td>+0.2</td>
</tr>
<tr>
<td>16</td>
<td>20.1</td>
<td>65.9</td>
<td>3.9</td>
<td>61.9</td>
<td>34.1</td>
<td>85.2</td>
<td>+0.3</td>
</tr>
<tr>
<td>18</td>
<td>20.6</td>
<td>74.3</td>
<td>5.0</td>
<td>69.3</td>
<td>25.7</td>
<td>85.5</td>
<td>+3.1</td>
</tr>
<tr>
<td>20</td>
<td>21.7</td>
<td>81.2</td>
<td>6.3</td>
<td>74.9</td>
<td>18.8</td>
<td>86.2</td>
<td>+8.4</td>
</tr>
<tr>
<td>22</td>
<td>23.0</td>
<td>87.2</td>
<td>7.3</td>
<td>79.8</td>
<td>12.8</td>
<td>87.0</td>
<td>+15.0</td>
</tr>
<tr>
<td>24</td>
<td>24.6</td>
<td>91.5</td>
<td>7.9</td>
<td>83.6</td>
<td>8.5</td>
<td>88.0</td>
<td>+22.9</td>
</tr>
</tbody>
</table>
Conclusions

• Do not blindly follow guidelines. Some current recommendations may inflate the patient’s risk and/or deteriorate power.

• Published frameworks can be applied without requiring the sponsor to perform own simulations – although they could further improve power based on additional assumptions.

• GSDs and TSDs are both ethical and economical alternatives to fixed sample designs.

• Recently the EMA’s BSWP – *unofficially!* – expressed some concerns about the validity of methods based on simulations.
(Adaptive) Sequential Two-Stage Designs

Outlook

• Selecting a candidate formulation from a higher-order crossover; continue with $2\times2\times2$ in the second stage.
• Continue a $2\times2\times2$ TSD in a replicate design for reference-scaling.
• Fully adaptive methods (taking the PE of stage 1 into account – without jeopardizing power).
• Exact methods (not relying on simulations).
Case Study 1

Potvin ‘Method C’ (2010 – 2011)

• Study stopped in stage 1
  – $AUC$: power $>$ 80%; passed BE with 90% CI.
  – $C_{max}$: power $<$ 80%; passed BE with 94.12% CI.

• NL: Adapting the confidence intervals based upon power is not acceptable and also not in accordance with the EMA guideline.* Confidence intervals should be selected \textit{a priori}, without evaluation of the power. Therefore, the applicant should submit the 94.12% confidence intervals for AUC.

  * What about: ‘… choice of how much alpha to spend at the interim analysis is at the company’s discretion.’?
  – Failed to show BE of $AUC$ with 94.12% CI.
  – Study repeated in India in a very (!) large fixed sample design.
  – Failed on $C_{max}$. Project cancelled.
Case Study 2

Potvin ‘Method C’ (2011 – 2012)

- Study passed already in stage 1
  - CV in the interim 30.65%, $n_1$ 49.
  - 90% CI since power was 87.3%.

- **UK, IE:** Unadjusted $\alpha$ in stage 1 not acceptable.
  - Study passed with 94.12% CI as well (*post hoc* switch to ‘Method B’).

- **AT:** The Applicant should demonstrate that the type I error inflation, which can be expected from the chosen approach, did not impact on the decision of bioequivalence.*

  * Unofficial information: Potvin’s table contains only a cell for CV 30% and $n_1$ 48…
  - One million studies simulated based on the study’s CV and $n_1$.
  - Empiric Type I Error 0.0494 (95% CI: 0.0490 – 0.0498).
Case Study 3

Potvin ‘Method C’ (2012 – 2013)

  – Unofficial feedback (after consultation of AEMPS with the BSWP):
    – Potvin’s method is not valid in Europe.

• Question to the Spanish Agency (2013):
  [...] we’d like to ask about the current status of TSD BE study, [...] if the BE protocol with Potvin’s Method C is acceptable now [...].
  – Answer:
    – Potvin’s methods are not acceptable in EMA.
Rumors & Chinese Whispers (Part 1)

TSDs based on simulations

• One member of the PKWP (2015):
  – I made peace with these methods and accept studies – *if* the confidence interval is not *too* close to the acceptance limits.
  – Remark: *How close* is ‘not too close’?

• Assessor of ES, AT (2016):
  – Kieser/Rauch (2015) showed that the adjusted $\alpha_{adj}$ 0.0294 used by Potvin et al. is Pocock’s for *superiority*. The correct value for *equivalence* is 0.0304 (Jennison/Turnbull 1999).
  – Hence, all studies evaluated with a 94.12% CI in both stages are more conservative than necessary. At least these studies should not be problematic.
  – Remarks:
    One could confirm ~0.0304 for ‘Method B’ in simulations. However, it is a misconception that 0.0304 is ‘universally valid’ for equivalence. *Other* settings (GMR, power) require *other* values – even for ‘Type 1’ TSDs.
TSDs based on simulations

• Another member of the PKWP asked the BSWP *which* inflation of the Type I Error would be acceptable (2015). He gave 0.0501 as an example.
  – Answer: The TIE must not exceed 0.05.
  – Remark: Rounding of the CI as required by the GL leads to acceptance of studies (regardless the design) with CLs of 79.995% and/or 125.004% – which inflates the TIE up to 0.0508. The BSWP should mind its own business.

• One assessor (PT) saw a study rejected by one of his colleagues – although BE was shown (2016).
  – When asked why, the answer was:
    – According to the BSWP Potvin’s methods are not acceptable.
    – He was not aware of such a statement and asked for an official document.
    – Such a document does not exist but all statisticians in the agencies know this statement.
Rumors & Chinese Whispers (Part 1)

TSDs based on simulations

- Scientific Advice in SE (2016).
  - Simulations based on Fuglsang’s ‘Type 1’ TSD for Parallel Groups (2014).
  - Large $n_1$ (up to 125/group), homo- and heterogenous variances, potentially unequal group sizes due to drop-outs.
  - With $\alpha_{adj} 0.0274$ the maximum Type I Error was 0.04992.
  - Response:
    - According to the guideline, application of a TSD was accepted provided that the patient’s risk is maintained at or below 5%.
    - Confirmed that the statement about Potvin’s methods is not public. These types of TSDs are not proven in a strict sense.
    - However, it was acknowledged that the simulations covered a sufficient range of possible outcomes (unequal variances and drop-out rates).
    - [...] the empiric type I error rate should be evaluated with the real data (i.e., the actual group sizes and variances of the study).
The Assessor’s Dilemma

TSDs based on simulations

• If an assessor would like to accept TSDs he/she is facing a dilemma:
  – TSDs are stated in the GL and therefore, studies are submitted.
  – The BSWP does not ‘like’ methods based on simulations and prefers methods which demonstrate by an analytical proof that the patient’s risk is preserved – which seemingly don’t exist.
  – According to the BSWP even a TIE of 0.0501 is not acceptable.
  – With one million simulations the significance limit (>0.05) is 0.05036.
    – Most methods show a TIE below this limit (and many even <0.05).
    – However, with other seeds of the random number generator (slightly) different results are possible.
  – It would be desirable to assess whether a passing study (with a CI close to the AR) has a relevant impact on the patient’s risk.
• I developed an R-package (AdaptiveBE), which currently is evaluated by assessors in Portugal and Spain.
Package AdaptiveBE

Function check.TSD()

- Required:
  - Interim data (CV or MSE, $n_1$, PE or CI), data of the final analysis (CV or MSE, $N$, PE or CI), adjusted alpha(s), the type of the TSD (optionally futility rules).
  - Alternatively (i.e., if not given in the report) the CIs can be used to calculate the CVs and/or the PEs.

- Algorithm:
  - Based on the interim data and the study’s framework simulate one million studies in order to obtain the empiric Type I Error.
  - If the TIE $\leq 0.05$, stop. Can accept the applicant’s results.
  - If not, optimize $\alpha_{adj}$ with a target TIE of 0.05. Recalculate the study (interim – and optionally – final) and compare conclusions with the reported ones.
    - If conclusions agree, accept the study (increase of the TIE not relevant).
    - If not (reported passes and adjusted fails), calculate the increase of relative risk. Whether the study is accepted or not lies in the hands of the assessor.
Available at [https://github.com/Helmut01/AdaptiveBE](https://github.com/Helmut01/AdaptiveBE)

- Example 2 of Potvin’s ‘Method C’
  - The maximum TIE in Table I of in the reference is 0.0510 for CV 20%, $n_1$ 12.
  - I used the reported $MSE$s and sample sizes. The CV in the interim was with 18.21% close to the location of the maximum TIE.
  - The power-calculation was done by the shifted $t$-distribution like in the reference.
  - R-code
  ```r
  library(AdaptiveBE)
  check.TSD(Var1=c(0.032634, "MSE"), PE1=c(0.083960, "log"), n1=12,
             Var=c(0.045896, "MSE"), PE=c(0.014439, "log"), N=20,
             alpha0=0.05, alpha1=0.0294, alpha2=0.0294,
             type=2, GMR=0.95, pmetho"shifted")
  ```
Function check.TSD()

− Part of the output

TIE for specified α: 0.05062 (>0.05)
Applied adjustment is not justified.
Final analysis of pooled data (specified α2 0.0294)

94.12% CI: 88.45–116.38% (BE concluded)

Adjusted α 1, 2 : 0.050 | 0.02858, 0.02858
Adjusted CIs : 90.00% | 94.28%, 94.28%
TIE for adjusted α : 0.04992 (n.s. >0.05)
Final analysis of pooled data (adjusted α2 0.02858)

94.28% CI: 88.36–116.39% (BE concluded)

Since conclusions of both analyses agree, can accept the original analysis.
Package AdaptiveBE

- It was difficult to fabricate an example where the original evaluation would pass and the optimized fail, i.e., a borderline case where the CI was ‘too close’ to the acceptance limits.
  - The maximum TIE reported in any of the publications is 0.0518 (Montague’s ‘Method D’, CV 20%, n₁ 12).
  - I used the interim CV and n₁, a PE₁ of 0.92, and in the final analysis a higher CV (22.3%), a worse PE (0.88), and one drop-out in the second stage (N 45).
  - The power-calculation was done by the shifted t-distribution like in the reference.
  - R-code
    ```r
    library(AdaptiveBE)
    check.TSD(Var1=c(0.200, "CV"), PE1=c(0.92, "ratio"), n1=12,
              Var=c(0.233, "CV"), PE=c(0.88, "ratio"), N=45,
              alpha0=0.05, alpha1=0.028, alpha2=0.028,
              type=2, GMR=0.90, pmethod="shifted")
    ```
Package AdaptiveBE

Function check.TSD()

— Part of the output

TIE for specified $\alpha$: 0.05153 (>0.05)

Applied adjustment is not justified.

Final analysis of pooled data (specified $\alpha_2$ 0.028)

94.40% CI: 80.00–96.80% (BE concluded)

Adjusted $\alpha$ 1, 2 : 0.050 | 0.02709, 0.02709
Adjusted CIs : 90.00% | 94.58%, 94.58%
TIE for adjusted $\alpha$ : 0.04998 (n.s. >0.05)
Final analysis of pooled data (adjusted $\alpha_2$ 0.02709)

94.61% CI: 79.94–96.87% (failed to demonstrate BE)

Accepting the reported analysis could increase the relative consumer risk by ~3.1%.
Rumors & Chinese Whispers (Part 2)

Simulations vs. ‘analytical proof’

- In principle regulators prefer methods where the control of the TIE can be shown analytically.
  - Promising zone approach (Mehta/Pocock 2011).
    Wrong: Superiority / parallel groups / equal variances.
    Critized by Emerson et al. (2011).
  - Inverse normal method (Kieser/Rauch 2015).
    Wrong: Not a proof but a claim. *Slight* inflation of the TIE (0.05026) in the supplementary material’s simulations.
  - Inverse normal approach / maximum combination test implemented in the development release of R-package Power2Stage available at https://github.com/Detlew/Power2Stage
Rumors & Chinese Whispers (Part 2)

Simulations vs. ‘analytical proof’

• In principle regulators prefer methods where the control of the TIE can be shown analytically.
    Correct. But only two posters about BE so far (not published in a peer-reviewed journal).

• In the inverse normal approach one obtains two $p$-values (compatible with the GLs requiring a confidence interval?)

• Both in the inverse normal approach and with repeated CIs the final $\alpha$ is adapted based on the study’s data (compatible with the GLs ‘pre-specified $\alpha$’?)

• Either there is a proof (but not for the conditions in BE) or it is not published yet.
Rumors & Chinese Whispers (Part 2)

Simulations vs. ‘analytical proof’

  - Most proofs start with …

  \[
  \text{Let us assume parallel groups of equal sizes and normal distributed data with } \mu = 0 \text{ and } \sigma = 1
  \]

  … followed by some fancy formulas.

Do these cases ever occur in reality?  

Peter Bauer
Thank You!

Open Questions?

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