Group-Sequential and Two-Stage Designs

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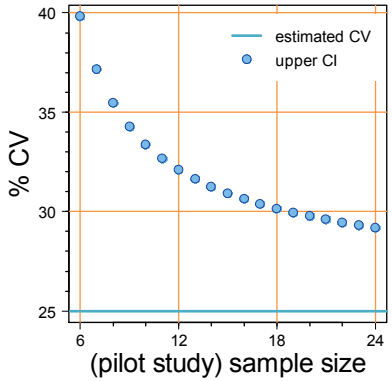
Dealing with Uncertainty

Nothing is 'carved in stone'.

- Never assume perfectly matching products.
  - Generally a Δ of not better than 5% should be assumed (0.950 – 1.053).
  - For HVD(P)s do not assume a Δ of <10% (0.900 – 1.111).
- Do not use the *CV* but one of its confidence limits.
  - Suggested α 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 α is possible, *i.e.*,
    a small α in the interim and a large one in the final analysis.
    Examples: Haybittle/Peto (α_1 0.001, α_2 0.049), O'Brien/Fleming (α_1 0.005, α_2 0.048), Zheng et al. (α_1 0.01, α_2 0.04).
    May require α-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 α is applied in both stages (regardless whether a study stops in the first stage or proceeds to the second stage).
    2. An unadjusted α may be used in the first stage, dependent on interim power.

Group-Sequential Designs

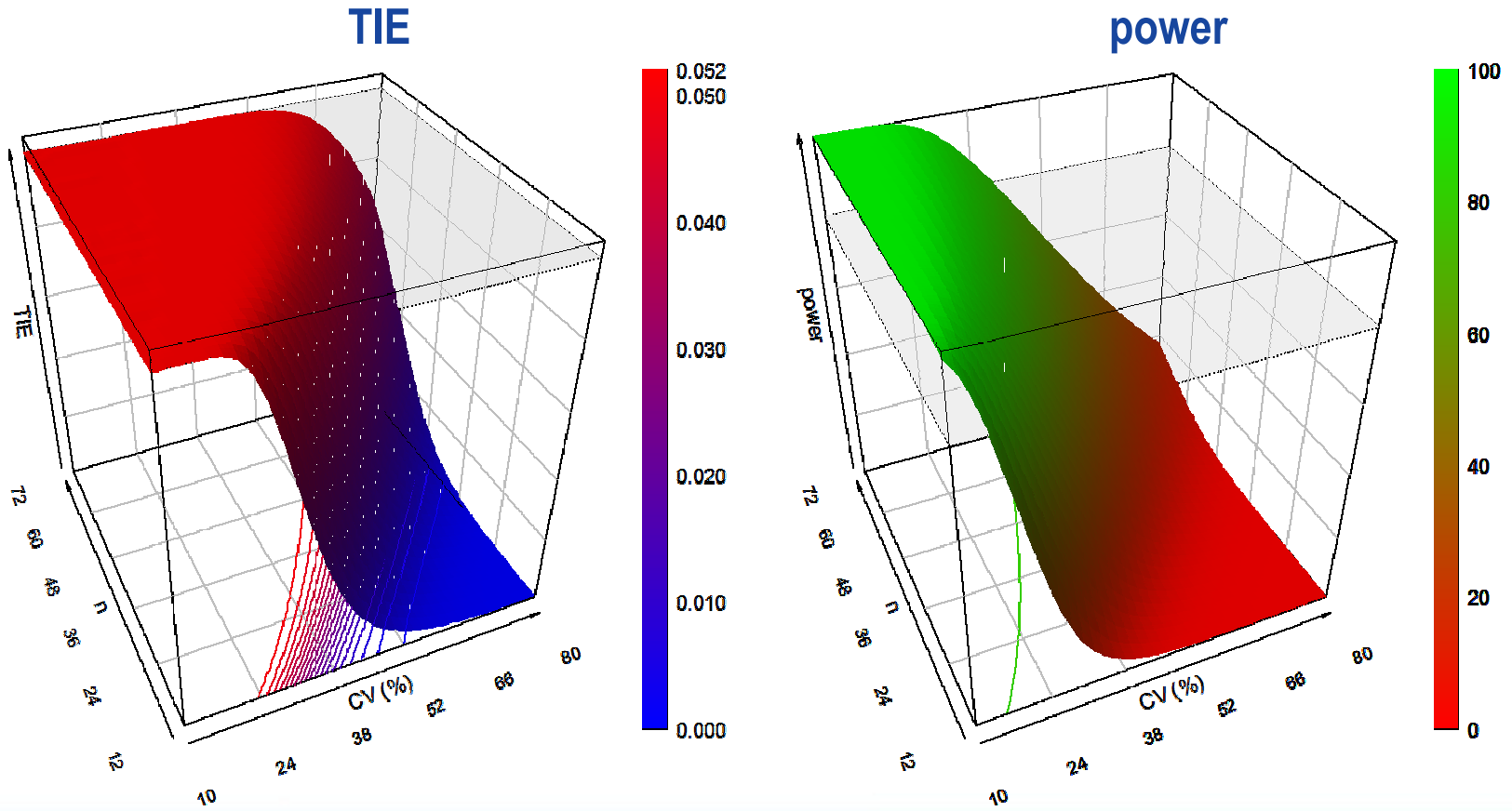
Long and accepted tradition in clinical research (phase III)

- Based on Armitage et al. (1969), McPherson (1974), Pocock (1977), O'Brien/Fleming (1979), Lan/DeMets (1983), Jennison/Turnbull (1999), …
  - Developed for superiority testing, parallel groups, normal distributed data with known variance, and interim at *N*/2.
  - First proposal by Gould (1995) in the field of BE did not get regulatory acceptance in Europe.
  - Asymmetric split of α is possible, *i.e.*,
    - a small α in the interim (*i.e.*, stopping for futility) and
    - a large one in the final analysis (*i.e.*, only small sample size penality).
    - Examples: Haybittle/Peto (α_1 0.001, α_2 0.049), O'Brien/Fleming (α_1 0.005, α_2 0.048).
    - *Not* developed for crossover designs and sample size re-estimation (fixed n_1 and variable *N*): Lower α_2 or α-spending functions (Lan/DeMets, Jennison/Turnbull) are needed in order to control the Type I Error.
    - Zheng et al. (2015) for BE in crossovers (α_1 0.01, α_2 0.04) controls the TIE.

Excursion

Type I Error and power

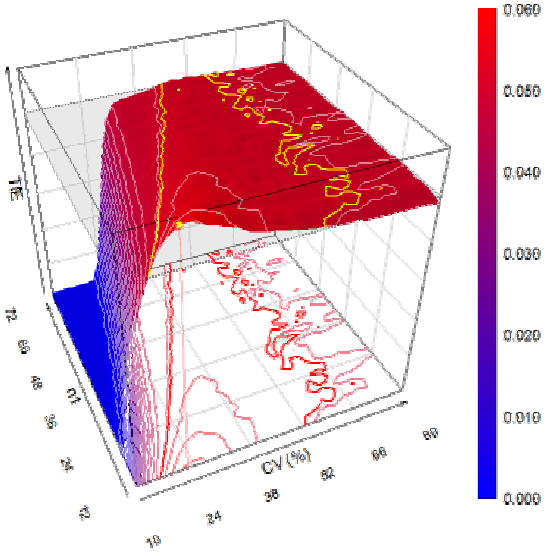
- Fixed sample 2×2×2 design (α 0.05). *GMR* 0.95, *CV* 10 – 80%, *n* 12 –72



Group-Sequential Designs

Type I Error

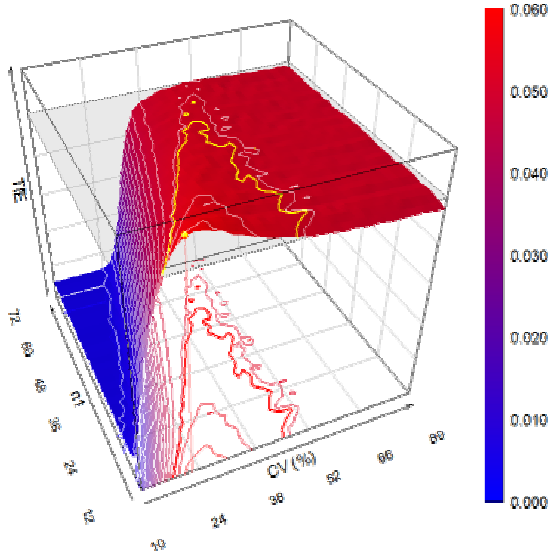
Haybittle/Peto
α_1 0.001, α_2 0.049



Maximum 0.05849

α_2 0.0413 needed
to control the TIE

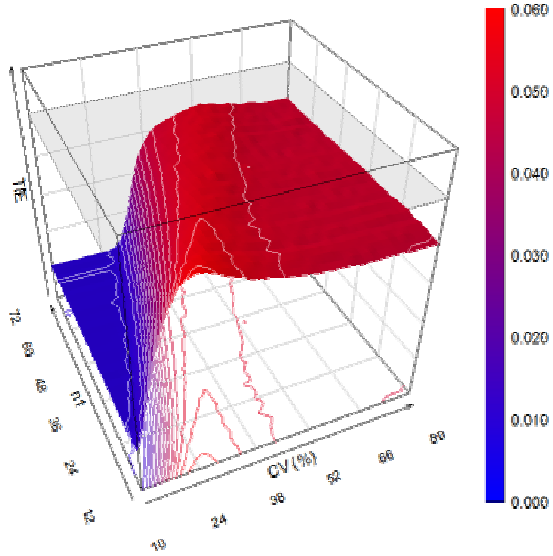
O'Brien/Fleming
α_1 0.005, α_2 0.048



Maximum 0.05700

α_2 0.0415 needed
to control the TIE

Zheng et al.
α_1 0.01, α_2 0.04



Maximum 0.04878

Group-Sequential Designs

Review of Guidelines

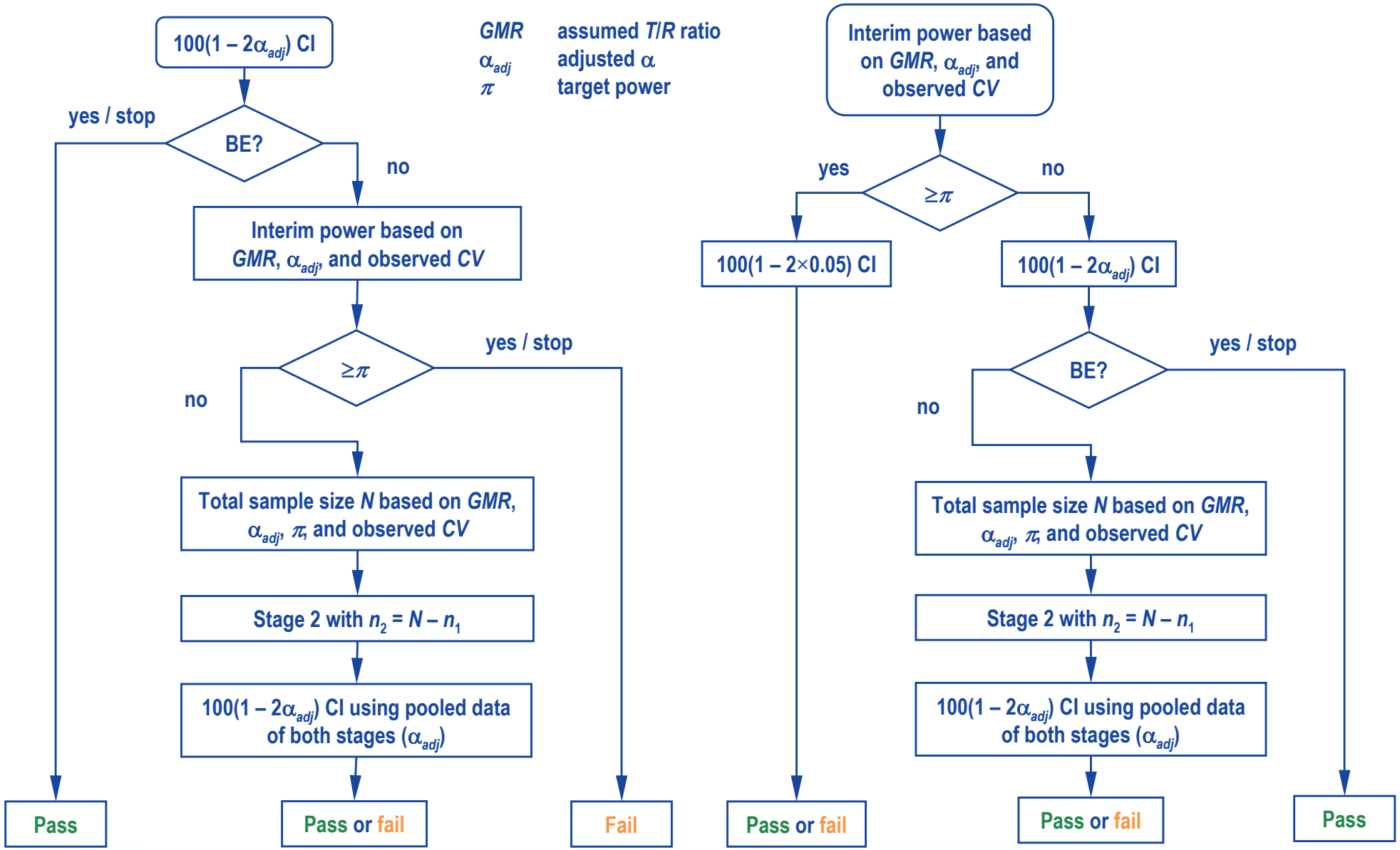
- Australia (2004), Canada (Draft 2009)
  - Application of Bonferroni's correction (α_{adj} 0.025).
  - Theoretical TIE ≤0.0494.
  - For *CV*s and samples sizes common in BE the TIE generally is ≤0.04.
- Canada (2012)
  - Pocock's α_{adj} 0.0294.
  - n_1 based on 'most likely variance' + additional subjects 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! α-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, *CV*s, *GMR*s, 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.

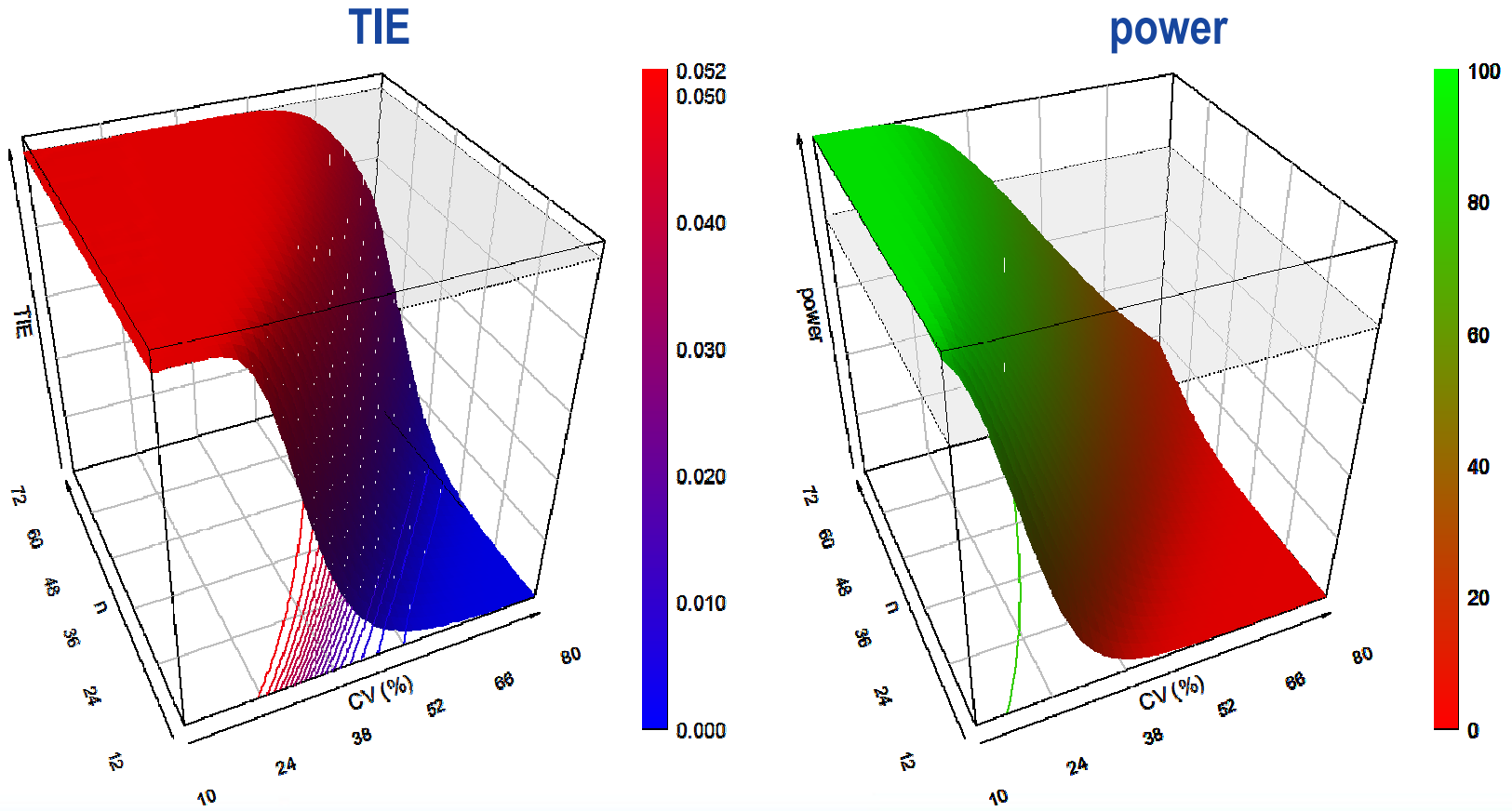
Type 1 and Type 2



Excursion

Type I Error and power

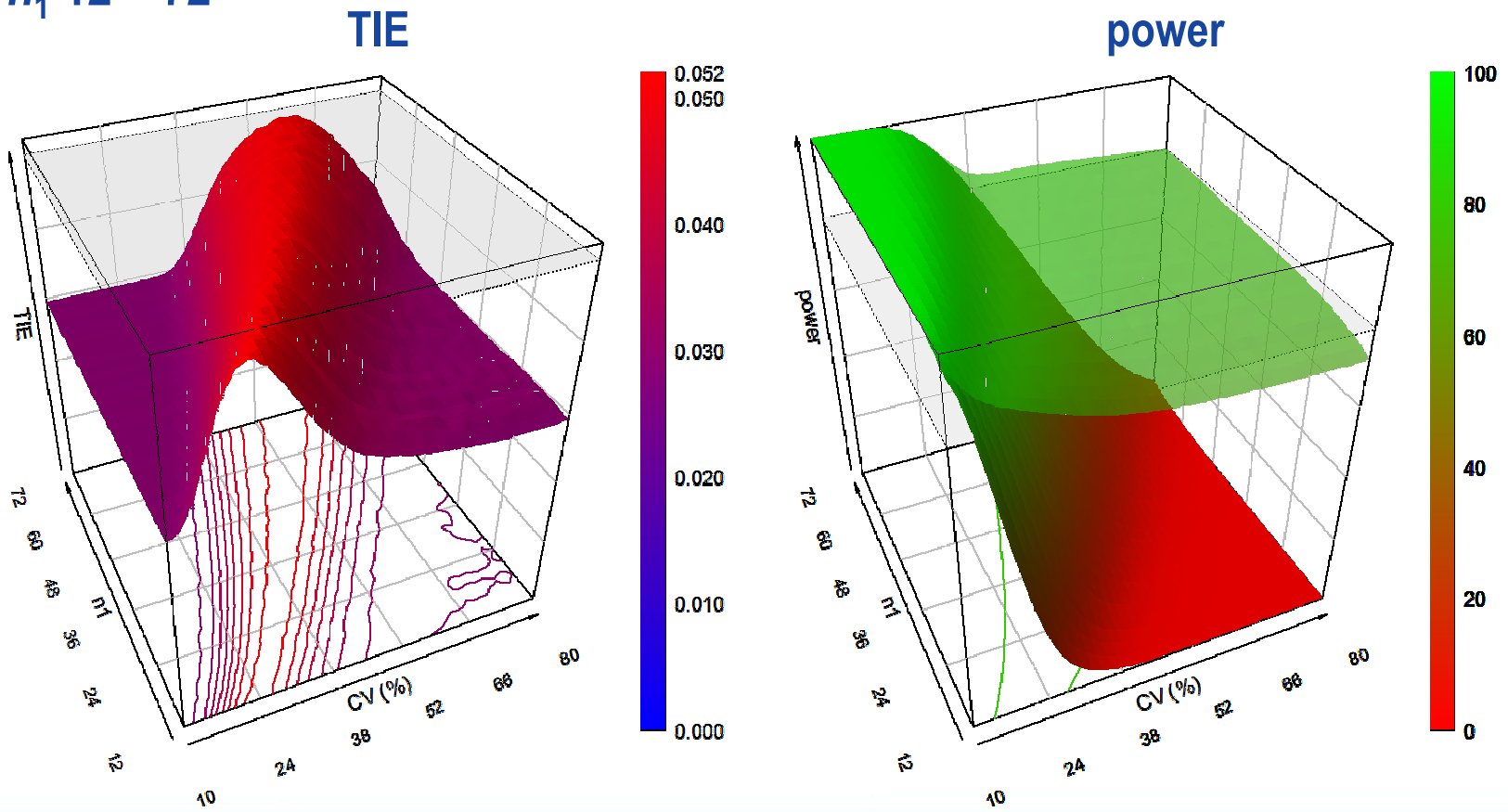
- Fixed sample 2×2×2 design (α 0.05). *GMR* 0.95, *CV* 10 – 80%, *n* 12 –72



Excursion

Type I Error and power

- 'Type 1' TSD (Potvin Method B, α_{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 α_{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.

Reference	Type	Method	*GMR*	Target power	CV_w	α_{adj}	TIE_{max}
Potvin *et al.* (2008)	1	B	0.95	80%	10 – 100%	0.0294	0.0485
	2	C					0.0510
Montague *et al.* (2012)	2	D	0.90			0.0280	0.0518
Fuglsang (2013)	1	B	0.95	90%	10 – 80%	0.0284	0.0501
	2	C/D				0.0274	0.0503
	2	C/D	0.90			0.0269	0.0501

- Xu *et al.* (2015). *GMR* 0.95, target power 80%, futility for the (1–2α_1) CI.

Type	Method	CV_w	Futility region	α_1	α_2	TIE_{max}
1	E	10 – 30%	0.9374 – 1.0667	0.0249	0.0363	0.050
2	F		0.9492 – 1.0535	0.0248	0.0364	0.050
1	E	30 – 55%	0.9305 – 1.0747	0.0254	0.0357	0.050
2	F		0.9350 – 1.0695	0.0259	0.0349	0.050

(Adaptive) Sequential Two-Stage Designs

Review of Guidelines

- EMA (Jan 2010)
  - Acceptable.
  - α_{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 α-spending functions or adaptive methods (where α_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):

    ```
    stage + sequence + sequence(stage) + subject(sequence × stage) +
    period(stage) + 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.

      ```
      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
      ```

(Adaptive) Sequential Two-Stage Designs

Review of Guidelines

- Health Canada (May 2012)
  - Potvin Method C recommended.
- FDA
  - Potvin Method C / Montague Method D recommended (Davit et al. 2013; 2nd GBHI conference, Rockville 2016).
- 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 α_{adj} and validating for TIE and power takes ~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 α 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).

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

(Adaptive) Sequential Two-Stage Designs

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 2×2×2 in the second stage.
- Continue a 2×2×2 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 *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 α 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)

- Protocol synopsis with statistical details submitted to the Spanish Agency (2012).
  - 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'?
- Assessors of ES, AT (2016):
  - Kieser/Rauch (2015) showed that the adjusted α_{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.

Rumors & Chinese Whispers (Part 1)

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 α_{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 α_{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.

Package AdaptiveBE

Available at 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

```
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, pmethod="shifted")
```

Package AdaptiveBE

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%, n_1 12).
  - I used the interim *CV* and n_1, a PE_1 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

```
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 α: 0.05153 (>0.05)
                     Applied adjustment is not justified.
Final analysis of pooled data (specified α2 0.028)
═══════════════════════════════════════════════════
94.40% CI: 80.00-96.80% (BE concluded)

Adjusted α 1, 2    : 0.050 | 0.02709, 0.02709
Adjusted CIs       : 90.00% | 94.58%, 94.58%
TIE for adjusted α : 0.04998 (n.s. >0.05)
Final analysis of pooled data (adjusted α2 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.
  - Repeated confidence intervals (Bretz et al. 2009). Adapted for BE (König et al. 2014, 2015).
    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 α is adapted based on the study's data (compatible with the GLs 'pre-specified α'?)
- 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'

- Summer Symposium *'To New Shores in Drug Development Implementing Statistical Innovation'*, Vienna, 27 June 2016
  - Most proofs start with …

    Let us assume parallel groups of equal sizes and normal distributed data with $\mu = 0$ and $\sigma = 1$

    … followed by some fancy formulas.

    Do these cases *ever* occur in *reality*? Peter Bauer

Group-Sequential and Two-Stage Designs

Thank You!

Open Questions?

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