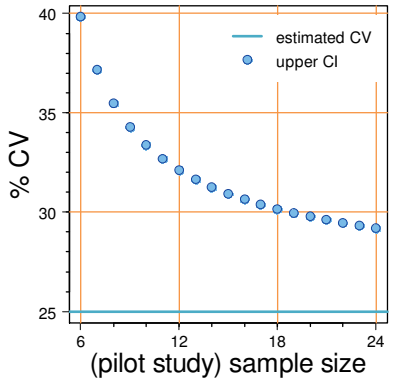
Two-Stage Sequential Designs

Helmut Schütz

Dealing with Uncertainty

Nothing is 'carved in stone'.

- 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 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.

Dealing with Uncertainty

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).

Dealing with Uncertainty

(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'
    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.
  - 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 keeping the TIE exist. It is the responsibility of the sponsor to demonstrate (*e.g.*, in simulations) that the consumer risk is preserved.

Excursion

Type I Error.

- In BE the Null Hypothesis (H_0) is *inequivalence*.
  - TIE = Probability of falsely rejecting H_0 (*i.e.*, accepting H_a and claiming BE).
  - In frameworks like Two-Stage Designs or reference-scaled ABE analytical solutions for power – and therefore, the TIE – are not possible. Hence, simulations are required.
    - Example: 2×2×2 crossover 'Type 1' TSD, *CV* 20%, n_1 12, α_{adj} 0.0294|0.0294, $\theta_0 = [\theta_1\ 0.80$ or $\theta_2\ 1.25]$, one million studies simulated.

```
library(Power2Stage)
AR <- c(1-0.20, 1/(1-0.20)) # common acceptance range: 0.80-1.25
power.2stage(CV=0.2, n1=12, alpha=rep(0.0294, 2),
             theta0=AR[1], nsims=1e6)$pBE
[1] 0.046508
power.2stage(CV=0.2, n1=12, alpha=rep(0.0294, 2),
             theta0=AR[2], nsims=1e6)$pBE
[1] 0.046262
```

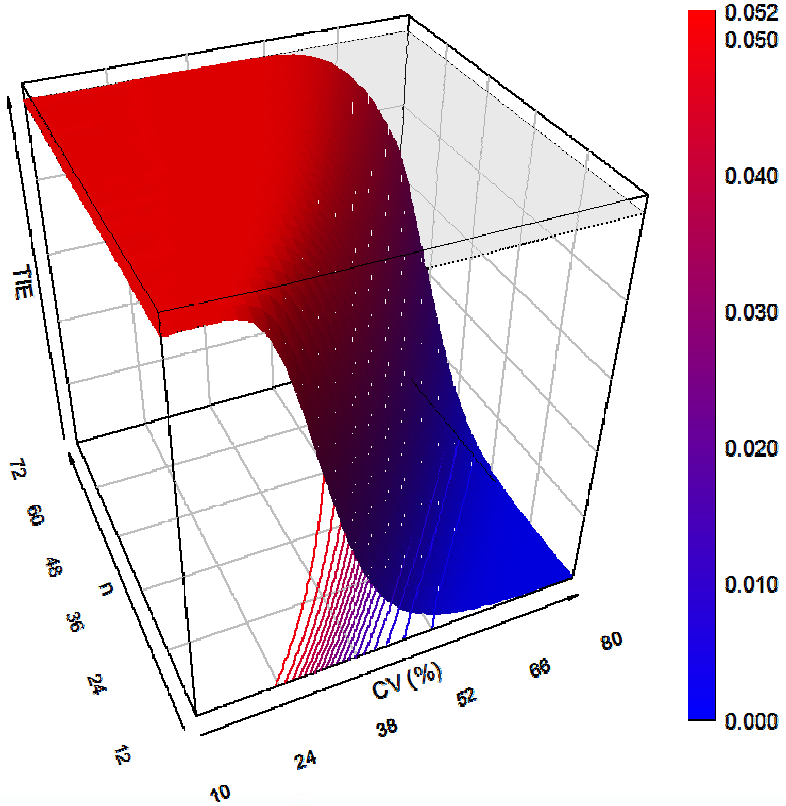
Labes D, Schütz H. *Power2Stage: Power and Sample-Size Distribution of 2-Stage Bioequivalence Studies*. R package version 0.4-3. 2015. https://cran.r-project.org/package=Power2Stage

Excursion

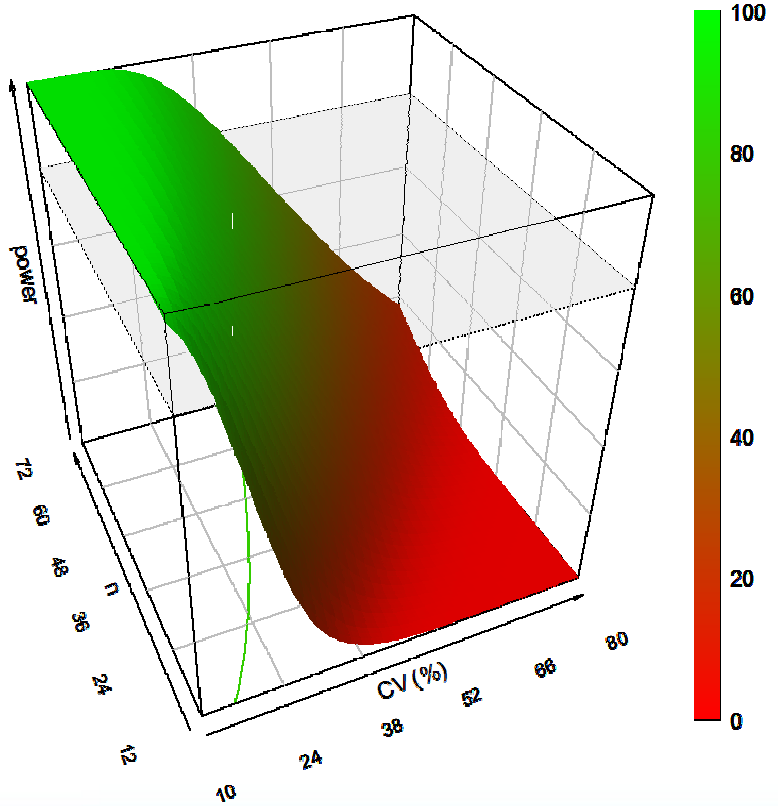
Type I Error and power.

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

TIE



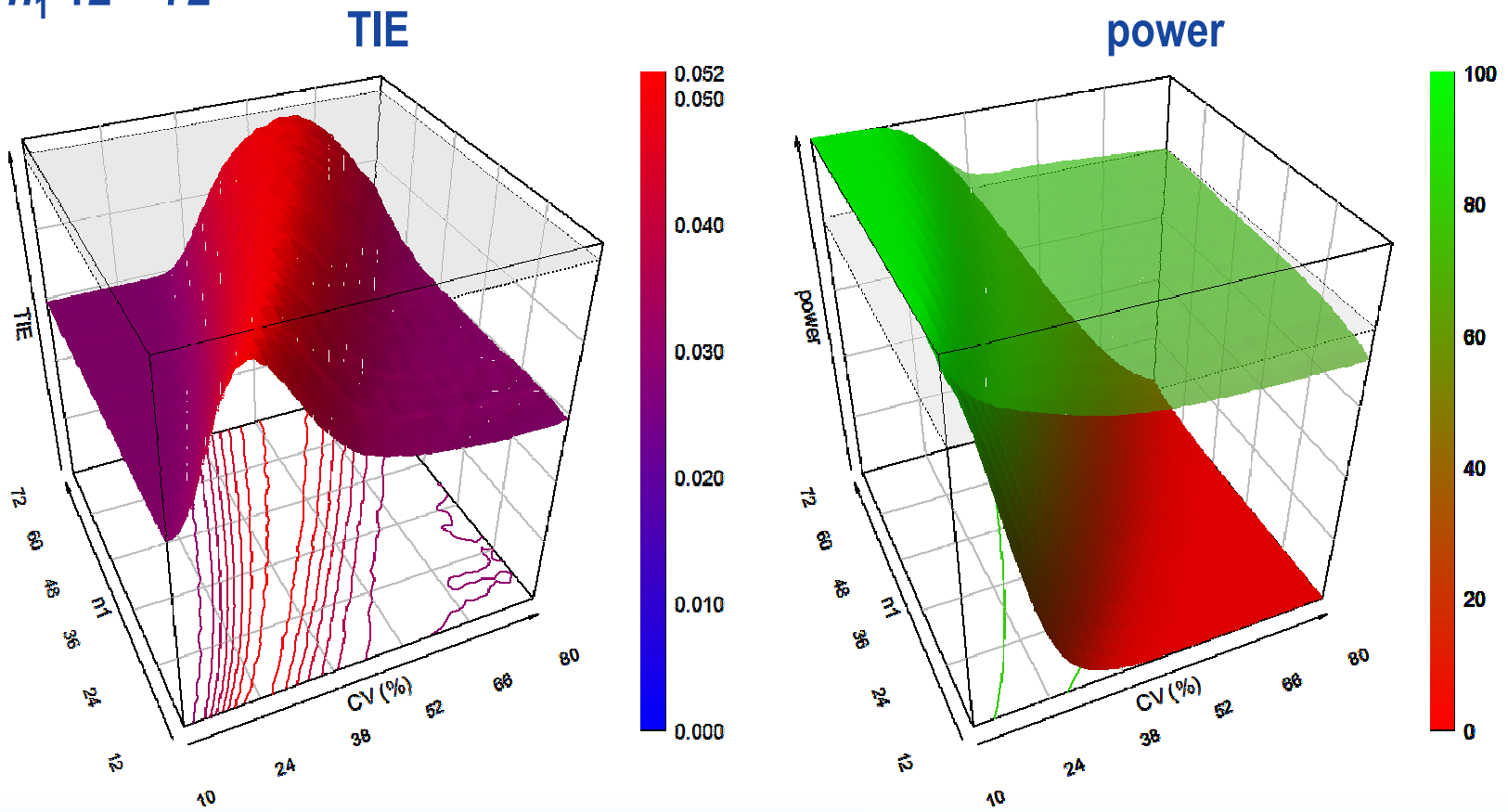
power



Excursion

Type I Error and power.

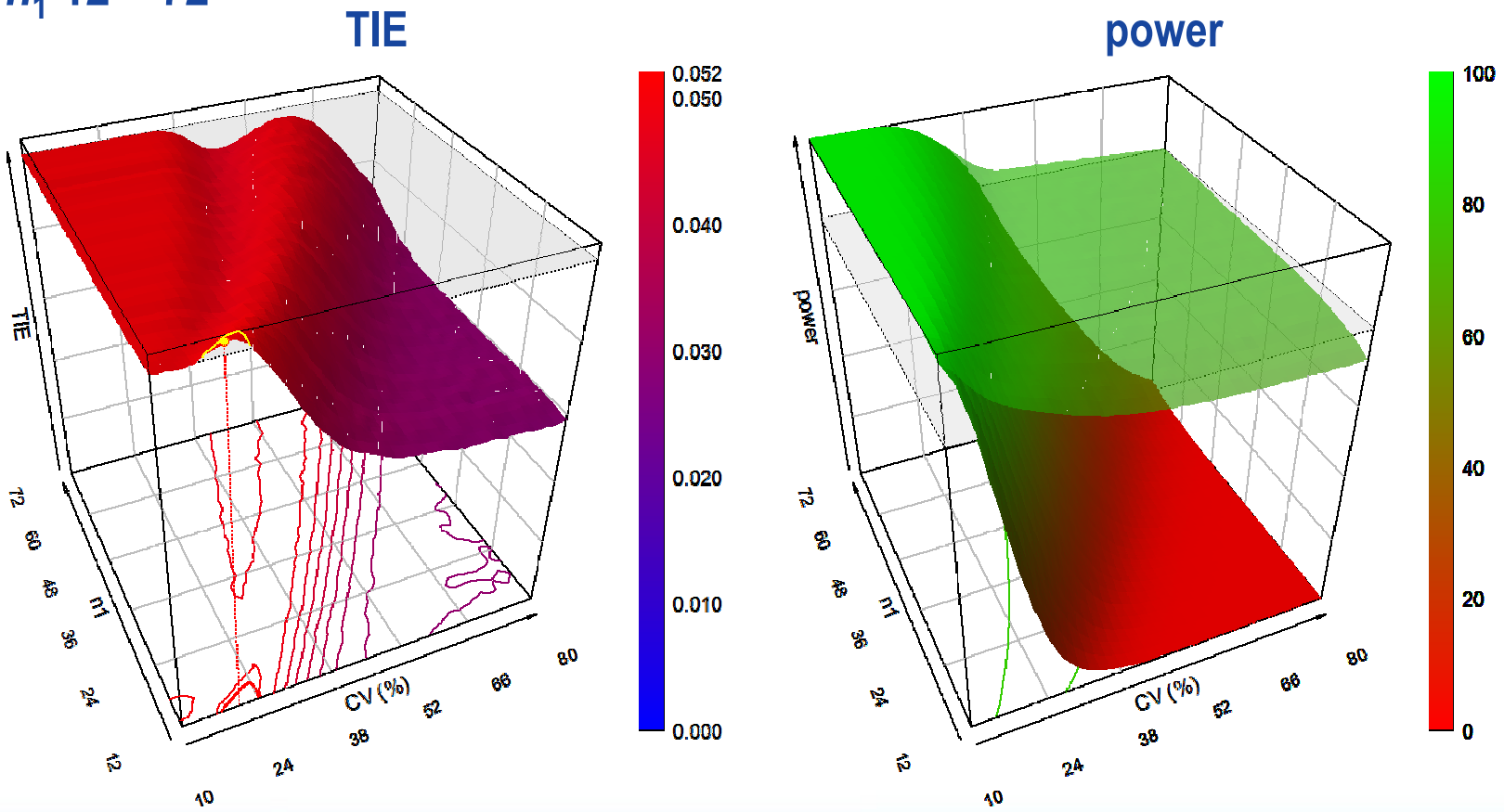
- 'Type 1' TSD (Potvin Method B, α_{adj} 0.0294). *GMR* 0.95, *CV* 10 – 80%, n_1 12 – 72



Excursion

Type I Error and power.

- 'Type 2' TSD (Potvin Method C, α_{adj} 0.05|0.0294). *GMR* 0.95, *CV* 10 – 80%, n_1 12 – 72



Group-Sequential Designs

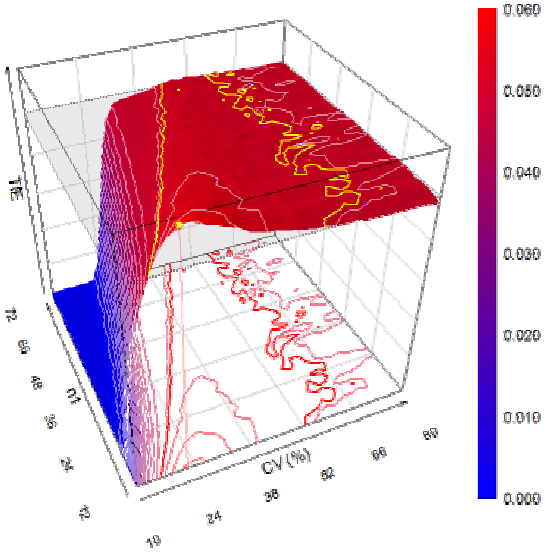
Long and accepted tradition in clinical research (phase III).

- 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) may be 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) keeps the TIE.

Group-Sequential Designs

Type I Error.

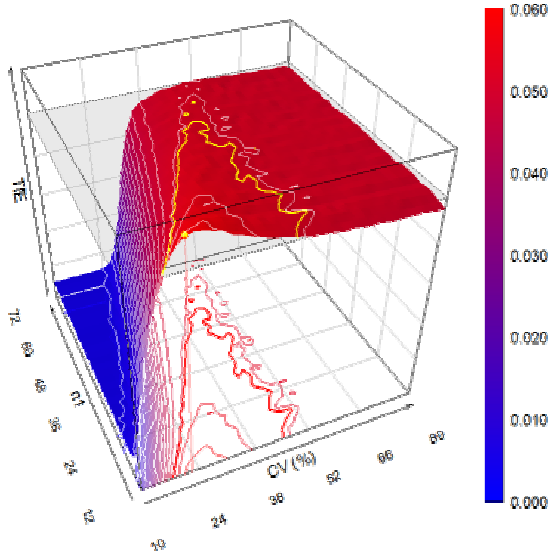
Haybittle/Peto
α_1 0.001, α_2 0.049



Maximum 0.05849

α_2 0.0413 needed
to control the TIE

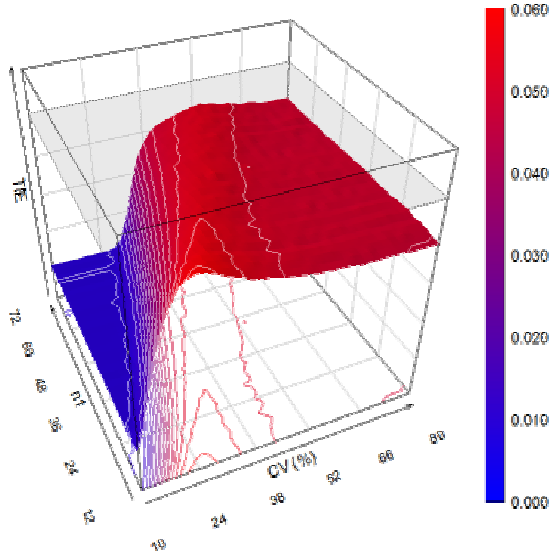
O'Brien/Fleming
α_1 0.005, α_2 0.048



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

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%).
  - Two 'Types'
    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.

(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 and Recommendations.

- 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 2016…

(Adaptive) Sequential Two-Stage Designs

Review of Guidelines and Recommendations.

- **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(CV=0.2, n1=12, theta0=1.25)$pBE
      [1] 0.046262
      power.2stage(CV=0.2, n1=12, theta0=1.25, min.n2=2)$pBE
      [1] 0.046262
      ```

(Adaptive) Sequential Two-Stage Designs

Review of Guidelines and Recommendations.

- Health Canada
  - Potvin Method C recommended (May 2012).
  - All simulation methods (B – F) acceptable (GBHI-meeting, Rockville Sep 2016).
- FDA
  - Potvin Method C / Montague Method D recommended (Davit et al. 2013).
  - All simulation methods (B – F) acceptable (GBHI-meeting, Rockville Sep 2016).
- Russia (2013)
  - 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.
  - State stopping criteria unambiguously 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 andKenward, 2014

  - Simulations straightforward with current software.
    - Finding a suitable α_{adj} and validating for TIE and power takes ~20 minutes with the open source R-package `Power2Stage`.

(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.

The EMA's concerns

Simulations *vs.* 'analytical proof'.

- In principle regulators prefer methods where control of the TIE can be shown analytically.
  - Promising zone approach (Mehta and Pocock 2011).
    Wrong Superiority / parallel groups / equal variances.
    Critized by Emerson et al. (2011).
  - Inverse normal method (Kieser and Rauch 2015).
    Wrong Not a proof but a claim. *Slight* inflation of the TIE (0.05026) in the supplementary material's simulations.
  - Repeated confidence intervals (Bretz et al. 2009).
    Adapted for bioequivalence (König et al. 2014, 2015).
    Correct But only two posters about BE so far (not published in a peer-reviewed journal).
- Either a proof exists (but *not* for the conditions in BE) or it is not published yet.

The EMA's concerns

Simulations *vs.* 'analytical proof'.

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

    Let us *assume* parallel groups of equal sizes and normal distributed data with means of 0 and variances of 1

    … followed by some fancy formulas.

    Do these cases *ever* occur in *reality*? Peter Bauer
- Is the BSWP not aware that rounding *already* inflates the TIE?

```
sprintf("%.5f%%", 100*CI.BE(pe=1.08076182, CV=0.30, n=24)[2])
[1] "125.00495%"
sprintf("%.2f%%", 100*CI.BE(pe=1.08076182, CV=0.30, n=24)[2])
[1] "125.00%"
sprintf("%.5f%%", 100*CI.BE(pe=1.08076182, CV=0.30, n=24,
                            alpha=0.0500434)[2])
[1] "125.00000%"
```

(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).

Two-Stage Sequential Designs

Thank You!

Open Questions?

Helmut Schütz

BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria

helmut.schuetz@bebac.at

References

Labes D, Schütz H, Lang B. *PowerTOST: Power and Sample size based on Two One-Sided t-Tests (TOST) for (Bio)Equivalence Studies*. R package version 1.4-2. 2016. https://cran.r-project.org/package=PowerTOST

Pocock SJ. *Group sequential methods in the design and analysis of clinical trials*. Biometrika. 1977;64:191–9.

Gould LA. *Group sequential extension of a standard bioequivalence testing procedure*. J Pharmacokinet Biopharm. 1995;23:57–86. DOI 10.1007/BF02353786

Haybittle JL. *Repeated assessment of results in clinical trials of cancer treatment*. Br J Radiol. 1971;44:793–7. DOI 10.1259/0007-1285-44-526-793

Peto R et al. *Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples*. Br J Cancer. 1977;35:2–39. DOI 10.1038/bjc.1977.1

O'Brien PC, Fleming TR. *A multiple testing procedure for clinical trials*. Biometrics. 1979;35:549–56.

Lan KG, DeMets DL. *Discrete sequential boundaries for clinical trials*. Biometrika. 1983;70:659–63.

Hauck WW, Preston PE, Bois FY. *A Group Sequential Approach to Crossover Trials for Average Bioequivalence*. J Biopharm Stat. 1997;71(1):87–96. DOI 10.1080/10543409708835171

Jennison C, Turnbull BW. *Equivalence tests*. In: Jennison C, Turnbull BW, editors. *Group sequential methods with applications to clinical trials*. Boca Raton: Chapman & Hall/CRC; 1999. p. 142–57.

Wittes J et al. *Internal pilot studies I: type I error rate of the naive t-test*. Stat Med. 1999;18(24):3481–91. DOI 10.1002/(SICI)1097-0258(19991230)18:24<3481::AID-SIM301>3.0.CO;2-C

Potvin D et al. *Sequential design approaches for bioequivalence studies with crossover designs*. Pharmaceut Statist. 2008;7(4):245–62. DOI 10.1002/pst.294

Bretz F, König F, Brannath W, Glimm E, Posch M. *Tutorial in biostatistics: Adaptive designs for confirmatory clinical trials*. Stat Med. 2009;28(8):1181–217. DOI 10.1002/sim.3538

Mehta CR, Pocock SJ. *Adaptive increase in sample size when interim results are promising: a practical guide with examples*. Stat Med. 2011;30(28):3267–84. DOI 10.1002/sim.4102

Emerson SS, Levin GP, Emerson SC. *Comments on 'Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples'*. Stat Med. 2011;30(28):3285–301. DOI 10.1002/sim.4271

Montague TH et al. *Additional results for 'Sequential design approaches for bioequivalence studies with crossover designs'*. Pharmaceut Statist. 2012;11(1):8–13. DOI 10.1002/pst.483

García-Arieta A, Gordon J. *Bioequivalence Requirements in the European Union: Critical Discussion*. AAPS J. 2012;14(4):738–48. DOI 10.1208/s12248-012-9382-1

Davit B et al. *Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences*. AAPS J. 2013;15(4):974–90. DOI 10.1208/s12248-013-9499-x

Karalis V, Macheras P. *An insight into the properties of a two-stage design in bioequivalence studies*. Pharm Res. 2013;30(7):1824–35. DOI 10.1007/s11095-013-1026-3

Karalis V. *The role of the upper sample size limit in two-stage bioequivalence designs*. Int J Pharm. 2013;456(1):87–94. DOI 10.1016/j.ijpharm.2013.08.013

Fuglsang A. *Futility rules in bioequivalence trials with sequential designs*. AAPS J. 2014;16(1):79–82. DOI 10.1208/s12248-013-9540-0

Fuglsang A. *Sequential Bioequivalence Approaches for Parallel Designs*. AAPS J. 2014;16(3):373–8. DOI 10.1208/s12248-014-9571-1

Karalis V, Macheras P. *On the Statistical Model of the Two-Stage Designs in Bioequivalence Assessment*. J Pharm Pharmacol. 2014;66(1):48–52. DOI 10.1111/jphp.12164

Golkowski D, Friede T, Kieser M. *Blinded sample size reestimation in crossover bioequivalence trials*. Pharmaceut Stat. 2014;13(3):157–62. DOI 10.1002/pst.1617

Jones B, Kenward MG. *Chapters 12–14*. In: Jones B, Kenward MG, editors. *Design and analysis of crossover trials*, Chapman & Hall/CRC; Boca Raton. 2014. p. 365–80.

Schütz H. *Two-stage designs in bioequivalence trials*. Eur J Clin Pharmacol. 2015;71(3):271–81. DOI 10.1007/s00228-015-1806-2

Zheng Ch, Zhao L, Wang J. *Modifications of sequential designs in bioequivalence trials*. Pharmaceut Statist. 2015;14(3):180–8. DOI 10.1002/pst.1672

Kieser M, Rauch G. *Two-stage designs for crossover bioequivalence trials*. Stat Med. 2015;34(16):2403–16. DOI 10.1002/sim.6487

König F, Wolfsegger M, Jaki T, Schütz H, Wasmer G. *Adaptive two-stage bioequivalence trials with early stopping and sample size re-estimation*. Trials. 2015;16(Suppl 2):P218. DOI 10.1186/1745-6215-16-S2-P218

Xu et al. *Optimal adaptive sequential designs for crossover bioequivalence studies*. Pharmaceut Statist. 2016;15(1):15–27. DOI 10.1002/pst.1721

Labes D, Schütz H. *Power2Stage: Power and Sample-Size Distribution of 2-Stage Bioequivalence Studies*. R package version 0.4-3. 2015. https://cran.r-project.org/package=Power2Stage