Introduction: Adaptive trials & sample size re-calculation

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Part of the training: ***Advanced group-sequential and adaptive confirmatory clinical trial designs, with R practicals using rpact***

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Learning objectives

- Fundamental statistical methodology of adaptive trials
  - p-value combinations and conditional error functions
  - CRP principle
  - Relation: group-sequential ↔ adaptive
  - Estimation and overall p-values
  - Conditional power and sample size adjustment
  - Guidance & recommendations

What are adaptive designs?

- Various «schools» of adaptive designs have developed in parallel, depending on the application area
- Our focus: Frequentist confirmatory adaptive designs
  - Predetermined or ad-hoc adaptations, of any trial features
  - Based on unblinded interim data and/or external information
- Excluded here:
  - Blinded design modifications (e.g. blinded sample size re-estimation)
  - Bayesian designs (frequent in early development phases)
  - Response-adaptive randomization; adaptive dose-escalation

Some definitions of adaptive designs

- Dragalin (PhRMA), 2006:
  - A multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial. [...] preplanning, as much as possible, based on intended adaptations.
- FDA draft guidance, 2010:
  - A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.
- EMA reflection paper, 2007:
  - A study is called 'adaptive' if statistical methodology allows the modification of a design element [...] at an interim analysis with full control of the type I error.
- FDA guidance, 2019:
  - A clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

Dragalin (2006); FDA (2010, 2019); EMA (2007)

Why adaptive designs

- In the 1980's, group sequential designs were introduced and grew popular. They provided a rigorous theory for early stopping but no other adaptations.
- In practice, however, adaptations of running trials were sometimes needed and done. Their impact on the inference was unclear and often ignored.
- Methods were needed to deal with this in a more rigorous way.

Ignition: Bauer (1989)

- Idea borrowed from meta-analysis (MA):
  - MA combines the inference from separate *trials*
  - Now: combine the inference from separate stages of one trial
  - This also allows adapting the second stage based on the first
- Method as well:
  - Take the product of the p-values from both trial stages
  - If $p_1 p_2$ is «too small» then reject H_0.
  - **Quiz**: What is «too small»?
    - Hint: How are p_1 and p_2 distributed under the null hypothesis?

Note: I use one-sided tests and p-values unless otherwise specified.

Bauer (1989)

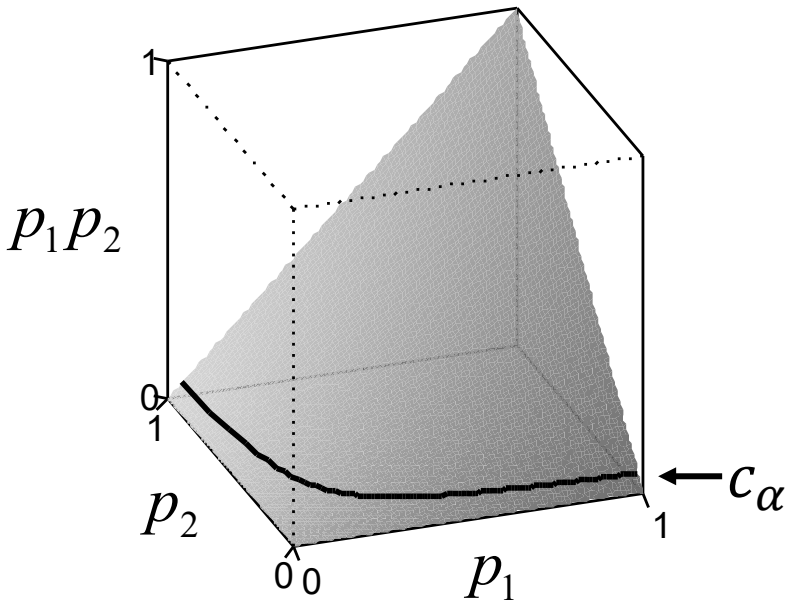
Fisher's product test

- $p_1, p_2 \sim_{H_0} U[0,1]$ iid
- $-2\ln(p_1), -2\ln(p_2) \sim_{H_0} \chi^2{}_2$ iid
- $-2(\ln(p_1) + \ln(p_2)) \sim_{H_0} \chi^2{}_4$
- Rejecting H_0 when $-2(\ln(p_1) + \ln(p_2)) \geq \chi^2{}_{4,1-\alpha}$ is a level α test
- Equivalently, rejecting H_0 when $p_1 p_2 \leq c_\alpha = \exp\left(-\frac{1}{2}\chi^2{}_{4,1-\alpha}\right)$

Fisher (1932)

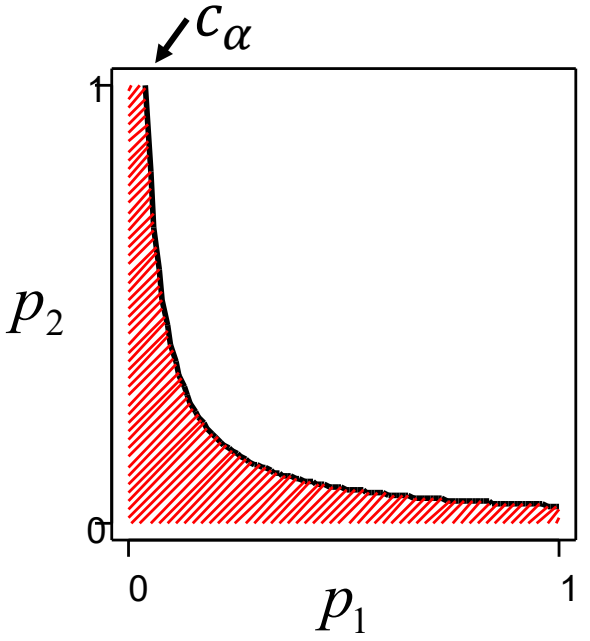
Let's look at it geometrically

- p-value combination



Reject if $p_1p_2 \leq c_\alpha$

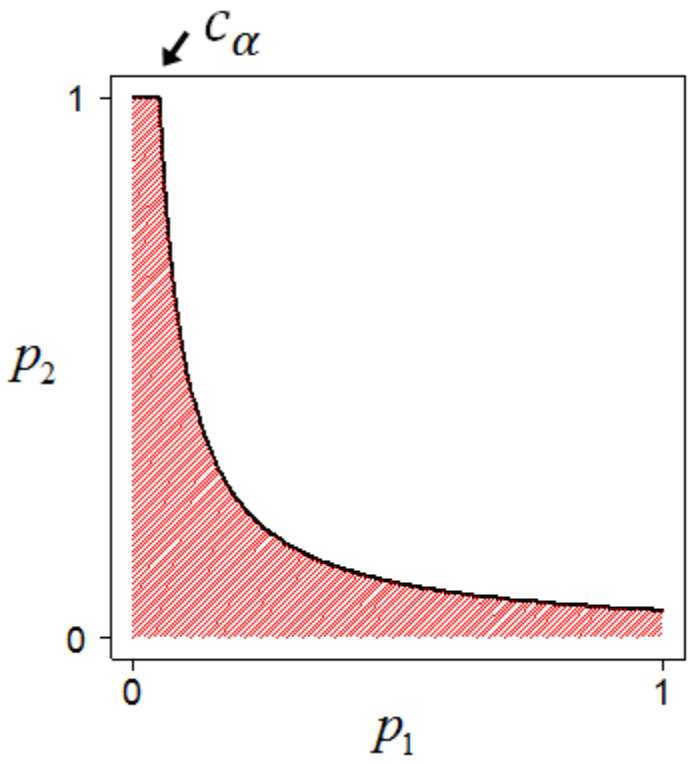
- Projection onto the plane



Reject if $p_2 \leq c_\alpha / p_1$

- **Quiz**: How large is the red area?

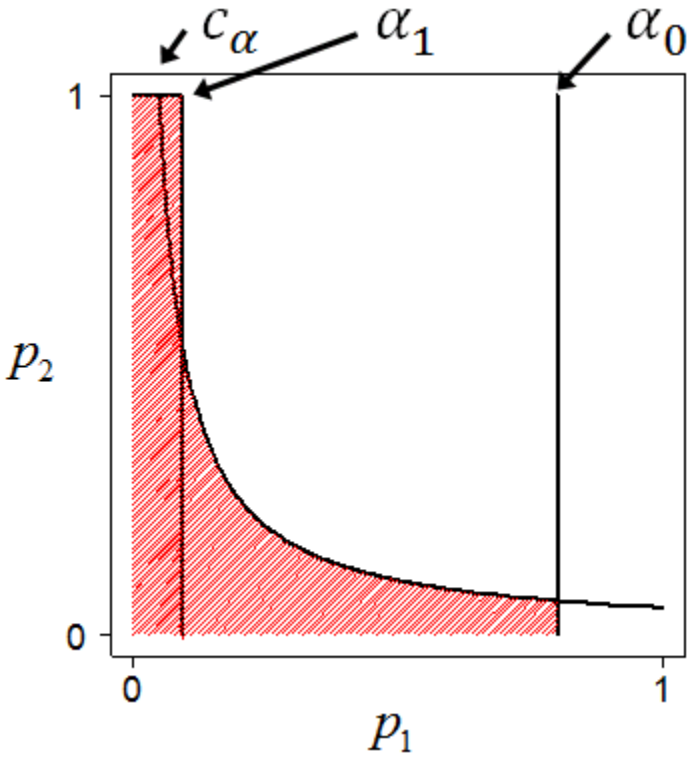
The conditional error function



- Area of rejection region:
  $\int_0^{c_\alpha} 1\, dp_1 + \int_{c_\alpha}^1 c_\alpha/p_1\, dp_1 = c_\alpha - c_\alpha \ln(c_\alpha)$
- But we know this must be α!
  - As $p_1, p_2 \sim_{H_0} U[0,1]$ iid, **areas correspond to probabilities**.
  - The rejection region has proba α.
- This level curve **defines** a level α test of H_0. It is called a conditional error function (c.e.f.).
- Every p-value combination defines a family of c.e.f.'s that fills the unit square, and vice versa.

Proschan, Hunsberger (1995); Posch, Bauer (1999); Wassmer (1999); Vandemeulebroecke (2006).

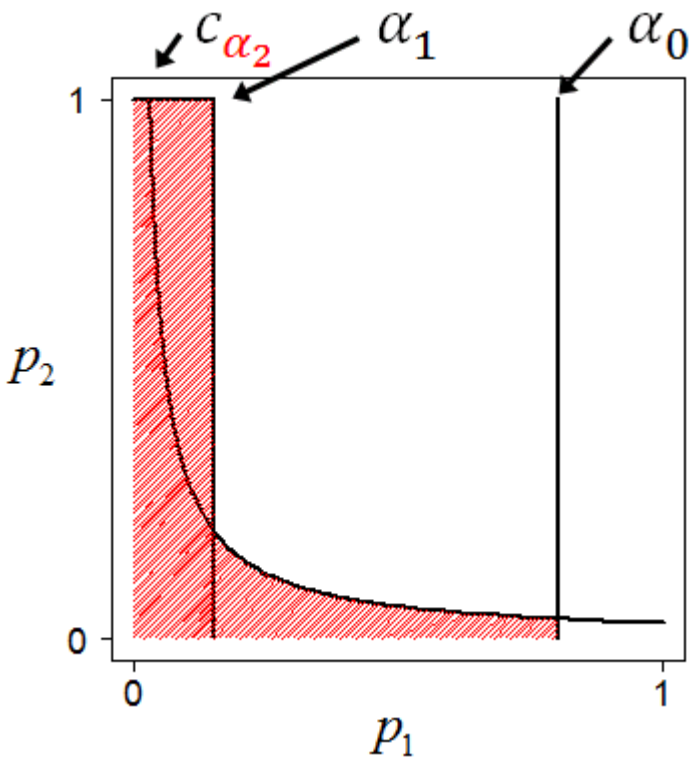
Early stopping



- Impose bounds α_1 and α_0
  - Assume $c_\alpha \leq \alpha_1 < \alpha_0$
  - $p_1 \leq \alpha_1$ → stop for efficacy
  - $p_1 > \alpha_0$ → stop for futility
  - Otherwise, perform second stage and reject H_0 if $p_2 \leq c_\alpha / p_1$
- Red area must remain α
  - $\alpha_1 + c_\alpha\left(\ln(\alpha_0) - \ln(\alpha_1)\right) = \alpha$

Bauer, Köhne (1994)

Change height of curve



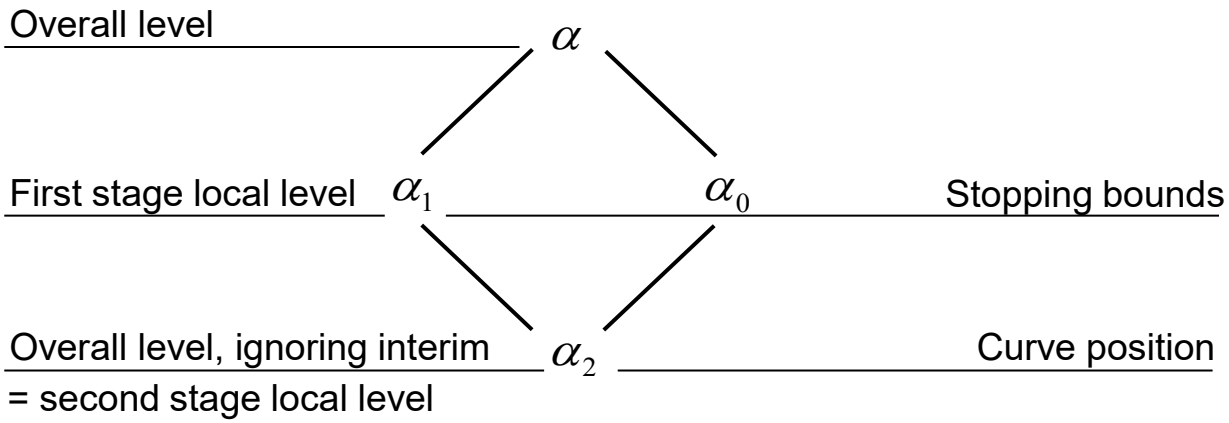
- Reject after second stage if $p_2 \leq c_{\alpha_2}/p_1$
  - This uses a different c.e.f. of the same family
  - The final test is performed at the local level α_2
- Red area must remain α

$$\alpha_1 + c_{\alpha_2}\big(\ln(\alpha_0) - \ln(\alpha_1)\big) = \alpha$$

Bauer, Röhmel (1995)

The «alpha calculus»

- Four parameters are interdependent



- Level condition: $\alpha_1 + c_{\alpha_2}\left(\ln(\alpha_0) - \ln(\alpha_1)\right) = \alpha$
- **Quiz**:
  - How would you specify a futility stop when control looks better?
  - How would you specify a «Pocock-type» test?

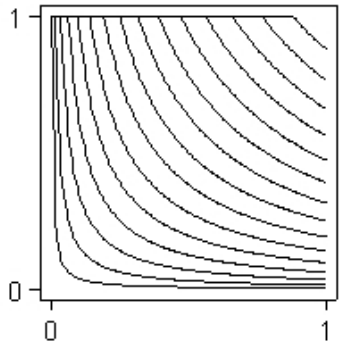
Vandemeulebroecke (2006)

Inverse normal method & more

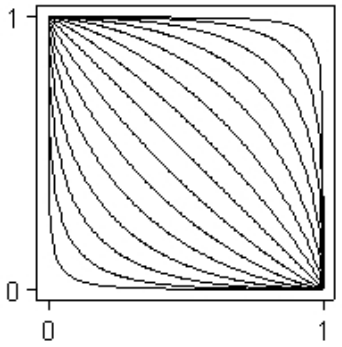
- Another natural way to combine p-values:

$$\frac{1}{\sqrt{2}}\left(\Phi^{-1}(1-p_1)+\Phi^{-1}(1-p_2)\right) \sim_{H_0} N(0,1)$$

- Same mechanism, with a different family of c.e.f.'s



Product test

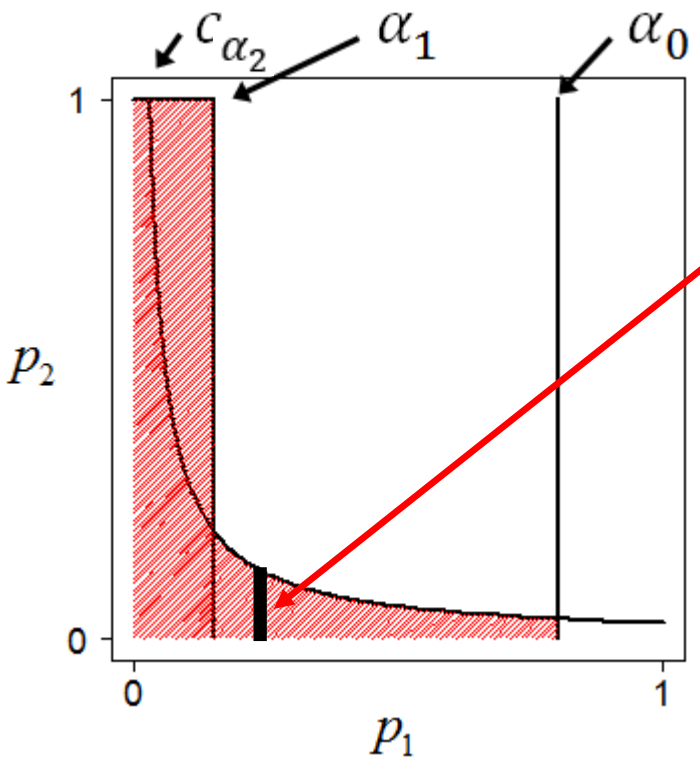


Inverse normal method (INM)

- In principle, any such family defines an adaptive test by this mechanism
  - In practice, mainly these two are used. And out of these, mostly INM.

Lehmacher, Wassmer (1999); Vandemeulebroecke (2006)

How do trial adaptations fit into this?



- This height is the Type I error probability given the first stage data
- We could now change the second stage into any design that respects this level
- The resulting overall procedure remains a level α test

Why does this work?

- For continuously distributed test statistics based on separate stages, p_1, p_2 will generally be iid $U[0,1]$ under H_0 even if the second stage is modified based on the interim analysis
- More generally, it still works if p_1, p_2 are only «p-clud»
  - $P_{H_0}(p_1 \leq u) \leq u$ and $P_{H_0}(p_2 \leq u \,|\, p_1) \leq u$ for all $u \in [0,1]$
- For more details on probabilistic foundations, see Brannath et al. 2012.

Brannath et al. (2002); Brannath et al. (2012)

Conditional Rejection Principle (CRP)

- Start with a (classical) level α test
- At an IA, review the data and possibly external information
- No reason to adapt → Continue as planned
- Reason to adapt

  → Compute cond. Type I error of the pre-defined design:

  $$P_{H_0}(\text{reject } H_0 \mid \text{interim data})$$

  And choose (based on all info) a new design at **this** level to finish the trial

- This is a level α test, and the IA need not be preplanned

Müller, Schäfer (2004)

Conditional Rejection Principle (CRP)

- How could that new second-stage design look like?
  - Increase the remaining sample size (e.g., to achieve a desired conditional power → *see later*)
    - Note: Health authorities view sample size **reductions** more critically
  - Replace the second stage by another two-stage design → multistage designs by «recursive combination»
  - ...and more
- Caveat
  - Adaptations must not jeopardize **interpretability** of results or **credibility** of the trial!

Müller, Schäfer (2004); Brannath et al. (2002)

Relation: Group sequ. ↔ adaptive

- Group sequential designs follow a cumulative philosophy: their test statstics are cumulative
- Adaptive designs follow a stagewise philosophy: they use stagewise inferences (test statistics, p-values)
  - However, the decision rules of adaptive designs combine the stagewise inferences – so overall **they do provide cumulative inference**
  - For example, Fisher's product test rejects H_0 if $p_2 \leq c_{\alpha_2}/p_1$
- The INM in particular reduces **exactly** to the group sequential test **if** no adaptations are done*. The test statistics, critical values and decision rules are identical.

→ *Next slide*

* ...and given some distributional assumptions.

Relation: Group sequ. ↔ adaptive

- Test active vs. placebo with normally distr. endpoint
- Group sequential: $X_{ki} \sim N(\mu, \sigma^2)$ iid, $Y_{ki} \sim N(\nu, \sigma^2)$ iid
  - $k = 1{,}2$ (stage); $i = 1, \ldots, n_k$; σ^2 known
  - $n = n_1 + n_2$ total sample size per arm; $n_1 = n_2$ without loss of generality
- The Z-test:
  - Overall: $Z = \sqrt{\frac{n}{2}} \frac{\bar{X} - \bar{Y}}{\sigma} \sim_{H_0} N(0,1)$
  - Per stage: $Z_k = \sqrt{\frac{n}{4}} \frac{\bar{X}_k - \bar{Y}_k}{\sigma} \sim_{H_0} N(0,1)$; $p_k = 1 - \Phi(Z_k)$
  - Group sequential: Using Z_1 and Z
  - Inverse normal method:

    Combining p_1 and p_2 to $\frac{1}{\sqrt{2}}\left(\Phi^{-1}(1-p_1) + \Phi^{-1}(1-p_2)\right) = \frac{1}{\sqrt{2}}(Z_1 + Z_2) = Z$

Relation: Group sequ. ↔ adaptive

- The INM therefore generalizes the group sequ. test
  - Standard group sequential software can be used
- It is easily communicated with commonly used (Z-) statistics
- It is also the uniformly most powerful test if no adaptations are done

➢ All this is why the INM is often the preferred method

Weights

- More general version of the INM
  - Combine stagewise statistics using $w_1 Z_1 + w_2 Z_2$ instead of $\frac{1}{\sqrt{2}}(Z_1 + Z_2)$, with weights w_k
  - Weights can be freely chosen under the constraint $w_1^2 + w_2^2 = 1$
  - But they must be prespecified and remain fixed regardless of adaptations
    - Otherwise, the type I error may be inflated
  - Natural choice: $w_k = \sqrt{\frac{n_k}{n_1 + n_2}}$
  - Then all patients carry equal weight, and again we have $w_1 Z_1 + w_2 Z_2 = Z$
  - The case $n_1 = n_2$ above was a special case of this

Efficiency vs. flexibility

- **Quiz:** What happens to the INM if we change the remaining sample size at the IA?
  - Not all patients carry equal weight → inefficient
- A curious debate
  - Tsiatis, Mehta (2003): "On the **inefficiency** of the adaptive design [...]"
  - Brannath et al. (2006): "On the **efficiency** of adaptive designs [...]"
- What do **you** think?
- In my view, trialists should weigh **efficiency** (power) against **flexibility** (adaptation)

Conditional power

- The conditional power is the power of the trial (at some alternative), given interim data
- Let's look at the inverse normal method
- Situation as before: $X_{ki} \sim N(\mu, \sigma^2)$ iid, $Y_{ki} \sim N(\nu, \sigma^2)$ iid
  - $k = 1,2$ (stage); $i = 1, \dots, n_k$
  - $n = n_1 + n_2$ total sample size per arm
  - Denote $\vartheta = \frac{\mu - \nu}{\sigma}$

→ *Next slide*

Proschan, Hunsberger (1995)

Conditional power

- $$CP_\vartheta = P_\vartheta\left(\frac{1}{\sqrt{2}}\left(\Phi^{-1}(1-p_1)+\Phi^{-1}(1-p_2)\right) \geq u_\alpha \,\middle|\, p_1\right)$$

$$= P_\vartheta\left(\frac{1}{\sqrt{2}}(Z_1+Z_2) \geq u_\alpha \,\middle|\, Z_1 = z_1\right)$$

$$= P_\vartheta\left(Z_2 \geq \sqrt{2}u_\alpha - z_1\right)$$

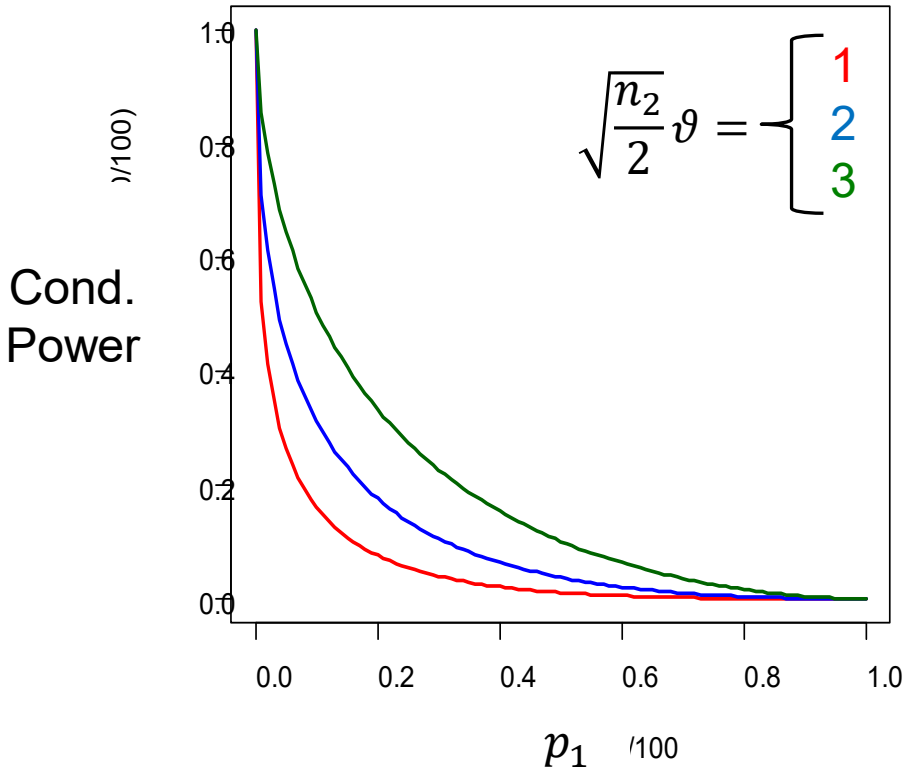
$$= P_\vartheta\left(Z_2 - \sqrt{\frac{n_2}{2}}\vartheta \geq \sqrt{2}u_\alpha - z_1 - \sqrt{\frac{n_2}{2}}\vartheta\right)$$

$$= 1 - \Phi\left(\sqrt{2}u_\alpha - z_1 - \sqrt{\frac{n_2}{2}}\vartheta\right)$$

Here, u_α is the $(1-\alpha)$-quantile of $N(0,1)$.

Conditional power

- Properties



- Conditional power
  - Increases with n_2
  - Increases with ϑ
  - Decreases for increasing p_1

Here, $\alpha = 0.025$

Conditional power

- Common applications
  - Stopping for futility if CP_ϑ is «too small» (e.g. below 20%)
  - Adjusting the second stage size to achieve a desired CP_ϑ (e.g. 90%)

    In the example, solve $0.9 = 1 - \Phi\left(\sqrt{2}u_\alpha - z_1 - \sqrt{\frac{n_2}{2}}\vartheta\right)$ for n_2

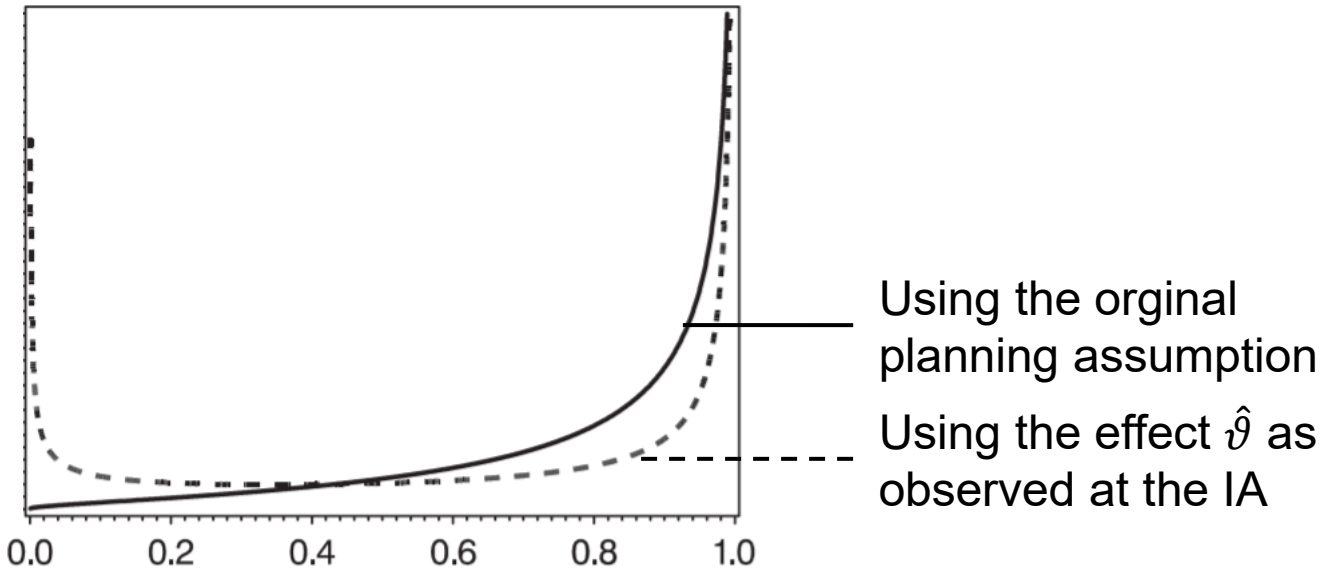
    Conduct the second stage and perform the final inference as planned through the adaptive design
- **Quiz**: What ϑ would you use in CP_ϑ?

Conditional power

- Several options for ϑ in CP_{ϑ}
  - The originally assumed effect size for sample size calculation (minimally clinically relevant effect – should not have changed!)
  - The effect size $\hat{\vartheta}$ as observed at the interim analysis (hoping that this comes closer to the «truth»)
    - **Caution**: Interim estimates such as $\hat{\vartheta}$ are notoriously volatile! → *Next slide*
  - Averaging across several choices
    - Weighted average of originally assumed and observed effect size
    - Integrating over some distribution for ϑ («predictive power»)

Conditional power

- Using the interim effect estimate is risky
  - Because we rely **doubly** on little data: through z_1 and through $\hat{\vartheta}$
  - The density of CP_{ϑ} tends towards extremes if we use $\hat{\vartheta}$



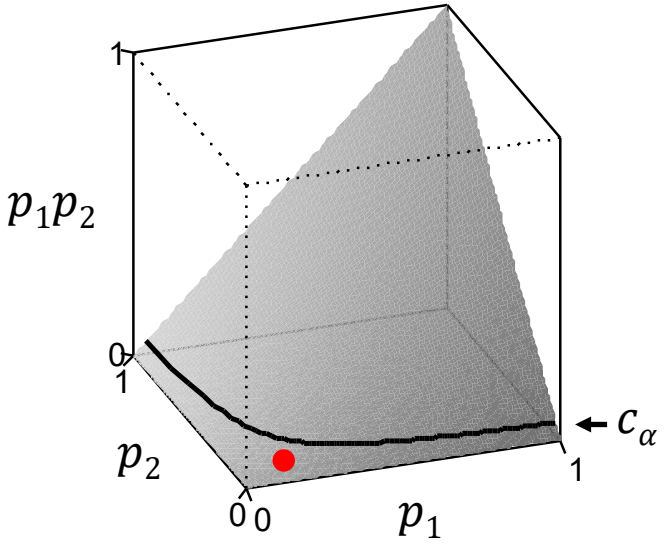
Here, $n_1 = n_2$, $\alpha = 0.025$, with 80% desired power. Bauer, König (2006)

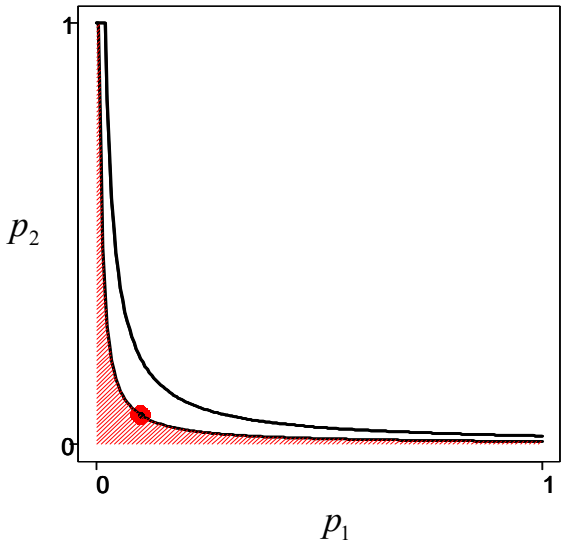
Estimation

- Naive maximum likelihood estimates are generally biased after an adaptive design
  - Because of early stopping
  - Because of adaptations
- For pre-specified adaptation rules, unbiased estimates can be constructed
- For ad-hoc adaptations, bias correction is not possible in general. Pragmatic solutions have been proposed, e.g.:
  - $\hat{\vartheta} = \tau\hat{\vartheta}_1 + (1-\tau)\hat{\vartheta}_2$ with pre-specified τ (e.g., $\tau = n_1/(n_1+n_2)$)
  - $\hat{\vartheta} = \tilde{\tau}\hat{\vartheta}_1 + (1-\tilde{\tau})\hat{\vartheta}_2$ with $\tilde{\tau} = \frac{w_1/se_1}{w_1/se_1 + w_2/se_2}$
    - Where se_k is the standard error of $\hat{\vartheta}_k$, and w_k are pre-specified weights such that ${w_1}^2 + {w_1}^2 = 1$
- Open field of research

Overall p-values

- Consider the product test to the level $\alpha = 0.1$
  - Reject H_0 if $p_1 p_2 \leq c_\alpha = 0.0205$
  - Observe $p_1 = 0.1$, $p_2 = 0.07$ → $p_1 p_2 = 0.007$ and we can reject H_0
  - **Quiz**: What is the overall p-value?
    - The null proba to observe outcomes «at least as extreme» as $(p_1, p_2) = (0.1, 0.07)$
    - Hint: Under H_0, p_1, p_2 iid $\sim U[0,1]$, and areas correspond to probabilities
    - Alternative interpretation: lowest level at which we would still be able to reject H_0





Regulatory guidance on unblinded sample size adaptation

EMA guidance on adaptive designs 2007

- The option to reassess sample size in an ongoing trial should not be seen as a substitute for careful planning. The relevance of a particular size of treatment effect should be discussed at the planning stage of the trial and not deferred to the point where interim results are already available.
- Whenever possible, methods for blinded sample size reassessment that properly control the type I error should be used […]. In cases where sample size needs to be reassessed based on unblinded data, sufficient justification should be made.

FDA adaptive designs guidance 2019

- [such designs] might be used when there is considerable uncertainty about the true treatment effect size.
- […] to appropriately control the Type I error […and] prospective planning […of] the statistical hypothesis testing method […and] the rule governing the sample size modification.
- […] additional challenges in maintaining trial integrity […]

Our recommendations for unblinded sample size adaptation

- Approach is accepted by health authorities, but more justification is needed than for blinded sample size adaptation
- Main application: Considerable uncertainty about the size of the treatment effect and reluctance to fund a group-sequential trial powered to the smallest clinically relevant effect size
  - *«Start small and invest more resources if results look promising»*
- Extensive clinical trials simulations and comparisons to group-sequential designs are highly recommended
  - Can also help to explore potential bias in estimation
  - **`rpact`** can produce median unbiased estimators and other inference adjusted for the adaptive design

Final thoughts on adaptive designs

- Allowance for adaptations of the trial design without inflating type I error
  - Adaptations should be pre-planned in most circumstances
  - ...but can be occasionally be used to react to unforeseen circumstances
- Can be extended to multi-arm and enrichment designs (covered later)
- Adaptive designs are more complicated than fixed or group-sequential designs in terms of trial planning, logistics, and regulatory requirements to ensure trial integrity and avoid operational bias
- Two attitudes:
  - The social event trial: «Let's come together, let's see and then adapt until significance» (Koch 2006)
  - Much better: «A multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial.» (Dragalin 2006)
- **Adaptive designs are not a remedy for sloppy planning!**

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- Barnes et al. (2010): Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. Pulmonary Pharmacology & Therapeutics 23: 165–171
- Schmoll et al. (2012): Cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as first-line treatment for patients with advanced colorectal cancer: A double-blind, randomized phase III study (HORIZON III). Journal of Clinical Oncology 30, 3588–3595
- Cuffe, Lawrence, Stone, Vandemeulebroecke (2014): When is a seamless study desirable? Case studies from different pharmaceutical sponsors. Pharmaceutical Statistics 13, 229–237

Software reviews

- Wassmer, Vandemeulebroecke (2006): A brief review on software developments for group sequential and adaptive designs. Biometrical Journal 48: 732–737
- Tymofyeyev (2014): A Review of Available Software and Capabilities for Adaptive Designs. Chapter in: Practical Considerations for Adaptive Trial Design and Implementation. Springer

Commercial software

- ADDPLAN: http://www.iconplc.com/innovation/addplan/
- EastAdapt and EastSurv: http://www.cytel.com/software/east

R packages

- adaptTest: https://cran.r-project.org/web/packages/adaptTest/index.html
- AGSDest: https://cran.r-project.org/web/packages/AGSDest/index.html
- asd: https://cran.r-project.org/web/packages/asd/index.html
- rpact: https://www.rpact.com/

BACKUP

The promising zone approach

- Chen et al. (2004) show that increasing the sample size with a conditional power of 50% or larger can be done with the classical Z-test without any inflation of the Type I error.
- Mehta and Pocock (2011) extended this idea to the Promising Zone Approach with a fixed sample size adaptation rule based on the estimated conditional power.
- Glimm (2012) showed that the Promising Zone Approach is a **conservative** application of the CRP principle. He and others (e.g. Jennison and Turnbull, 2015) also showed that the resulting sample size calculation rule is **inefficient**.

The «Constrained Promising Zone» (CPZ) Approach

- A recent proposal for a more refined use of conditional power to re-calculate the sample size
  - Builds upon the previously proposed «Promising Zone» approach by Mehta and Pocock (2011) which had been shown to be (overly) conservative (Glimm 2012, Jennison and Turnbull 2015)
- Idea: *Boost the sample size within reasonable limits when the interim treatment effect appears «promising»*

Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

The «Constrained Promising Zone» (CPZ) Approach

- Concretely, pre-specify:
  - Impose limits to allowed total sample size per arm: n_{min}, n_{max}
  - Set smallest clinically meaningful effect size ϑ_{min}, and smallest / largest desired conditional power at this point: CP_{min}, CP_{max}
  - Choose a combination test, e.g. INM with $w_1 = \sqrt{\frac{n_1}{n_{min}}}$, $w_2 = \sqrt{\frac{n_{min}-n_1}{n_{min}}}$
- Then re-calculate the sample size at the IA:
  - If n^* exists between n_{min} and n_{max} such that $CP_{\vartheta_{\min}}(z_1, n^*) = CP_{max}$, then set the total sample size (per arm) to n^*
  - Otherwise, if $CP_{\vartheta_{\min}}(z_1, n_{max}) \geq CP_{min}$, then set it to n_{max}
  - Finally, otherwise, set it to n_{min} because the IA is not «promising»

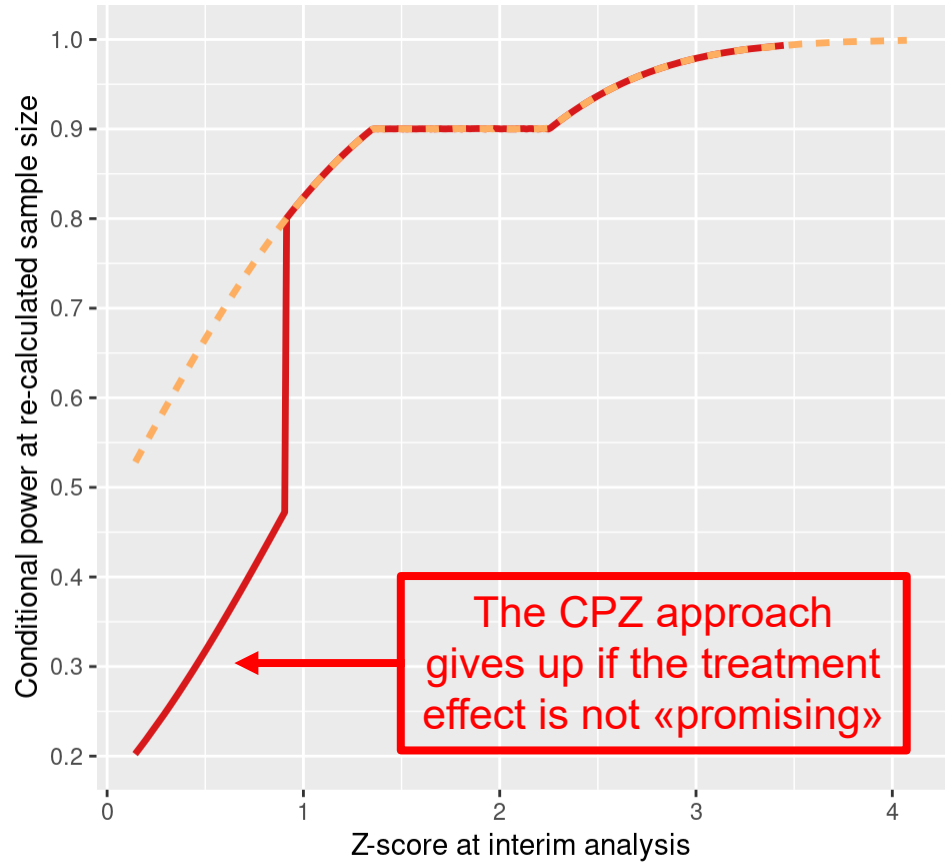
Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

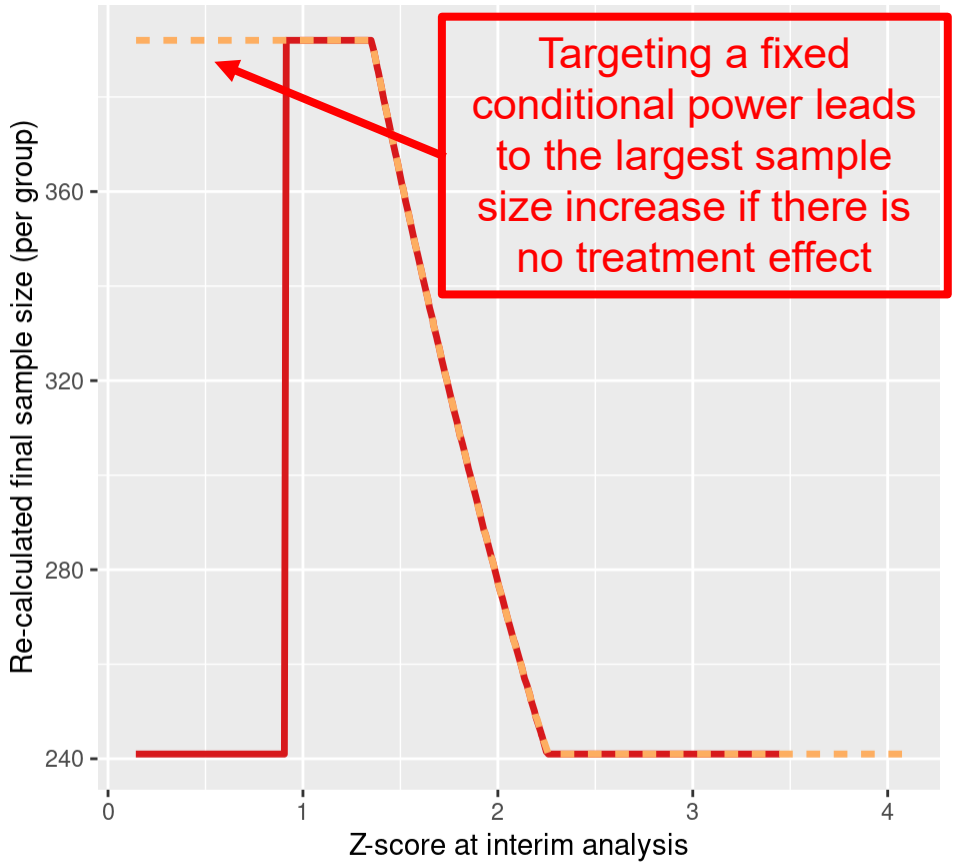
The «Constrained Promising Zone» (CPZ) Approach - Example

- 1:1 randomization with Overall Response Rate (ORR) as primary endpoint
  - ORR=20% on Control; Drug increases this by 10-13%
  - 2.5% significance level (one-sided)
  - $n_1 = 120$
  - $n_{min} = 241$, $n_{max} = 392$ (90% power for Δ=13% and Δ=10%, resp.)
- Compare two approaches
  - Sample size increase for a conditional power of 90% (if true Δ=10%)
  - CPZ design with $CP_{min} = 80\%$, $CP_{max} = 90\%$
- Corresponding R-code is in this vignette
  - Simulation of a Trial with a Binary Endpoint and Unblinded Sample Size Re-Calculation with rpact

Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

Cond. power and total sample size depending on the interim Z-score

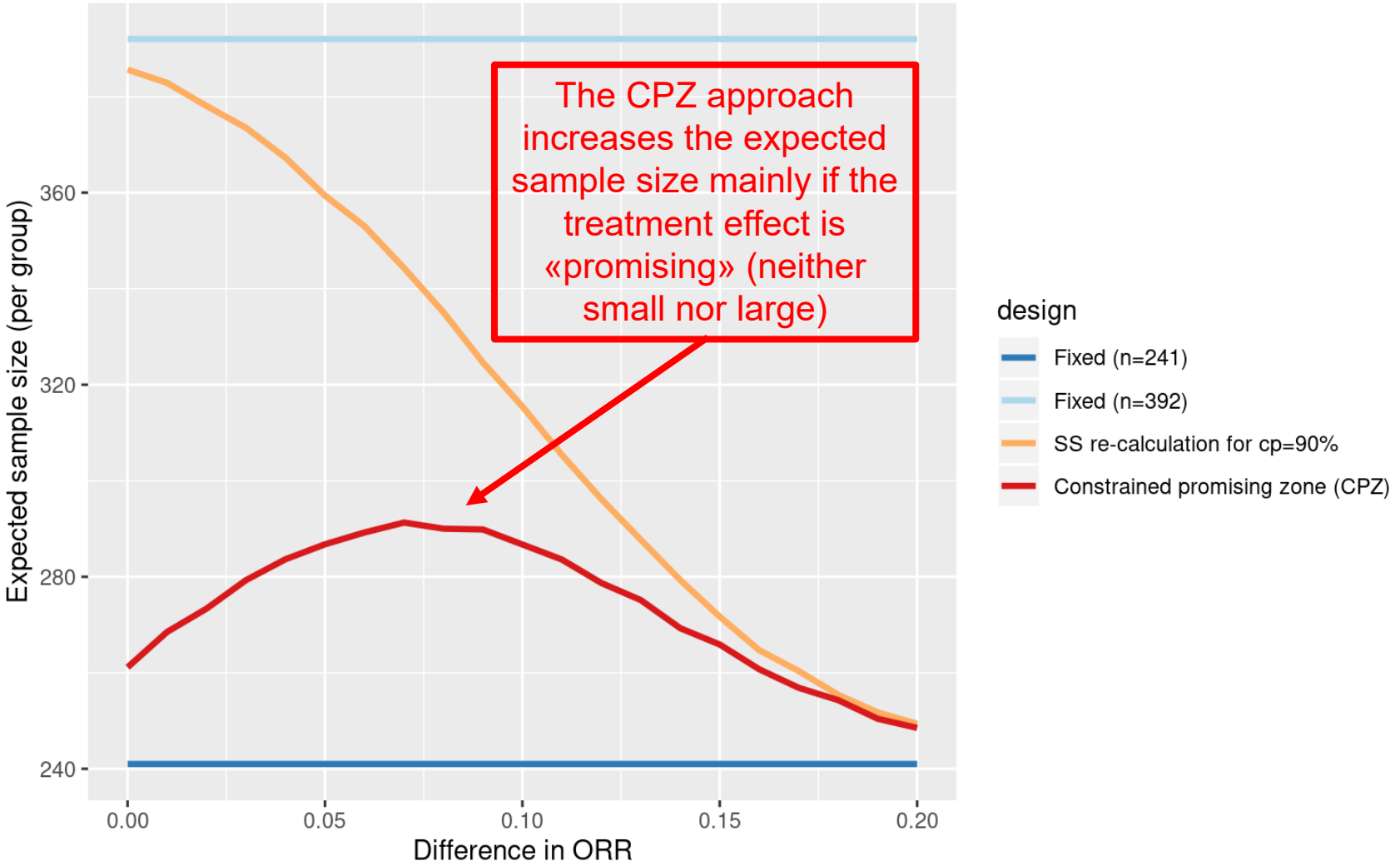




design — Constrained promising zone (CPZ) — SS re-calculation for cp=90%

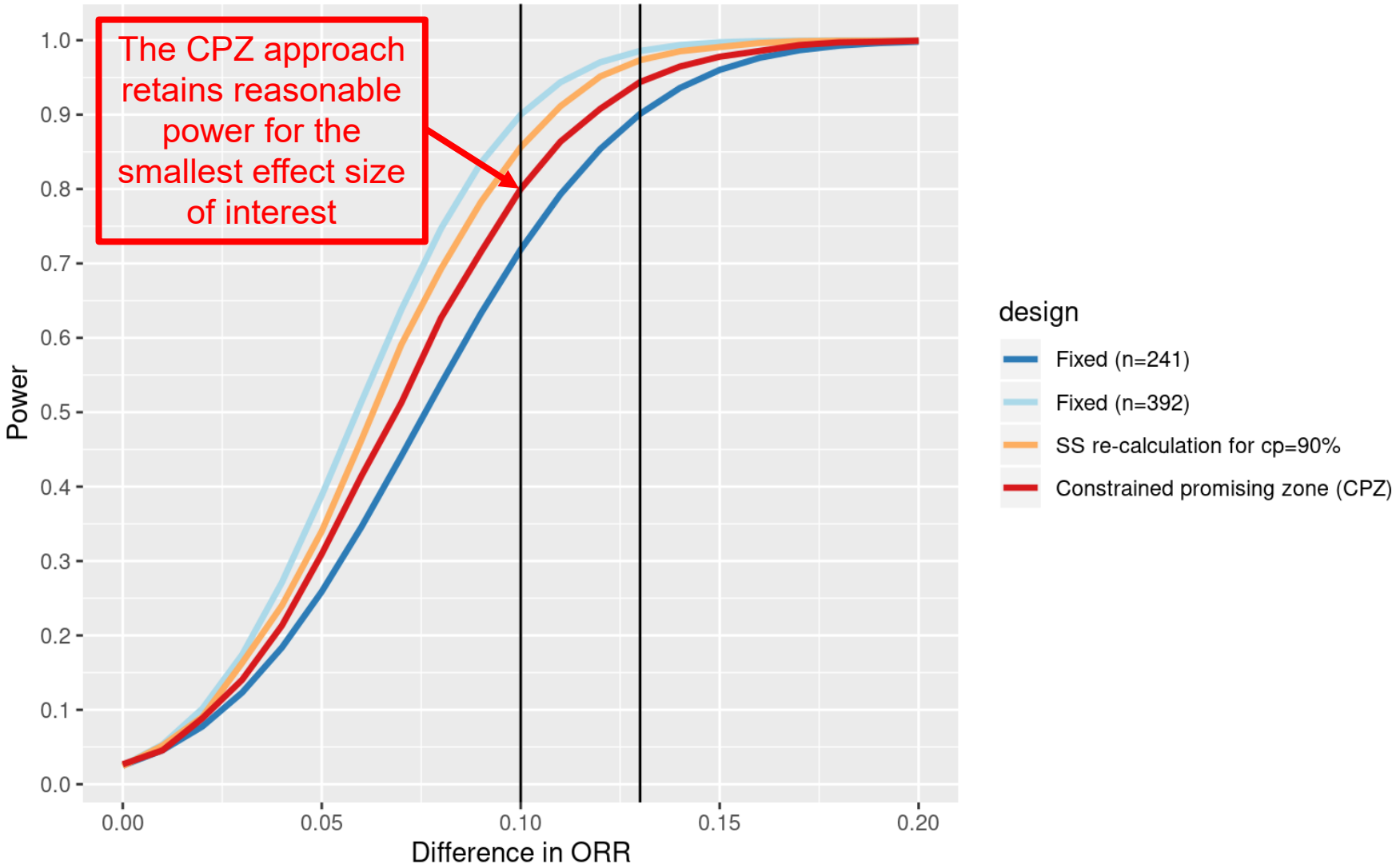
Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

Expected sample size depending on effect size



Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

Power depending on effect size



Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

What are adaptive designs?

*Adaptive **randomization***

- Treatment allocation probabilities are modified during the trial. Main types:
  - Allocation depends on past assignments (e.g. biased coin design, Efron 1971)
    - Goal: Balance treatment allocation over time
  - Allocation depends on covariates and past assignments (e.g. Minimization, Pocock and Simon 1975)
    - Goal: Balance treatment allocation within subgroups
  - Allocation depends on prior responses (e.g. Play-the-winner, Wei and Durham 1978)
    - Goal: Assign patients with greater likelihood to efficacious treatments
  - Combinations of the above...

What are adaptive designs?

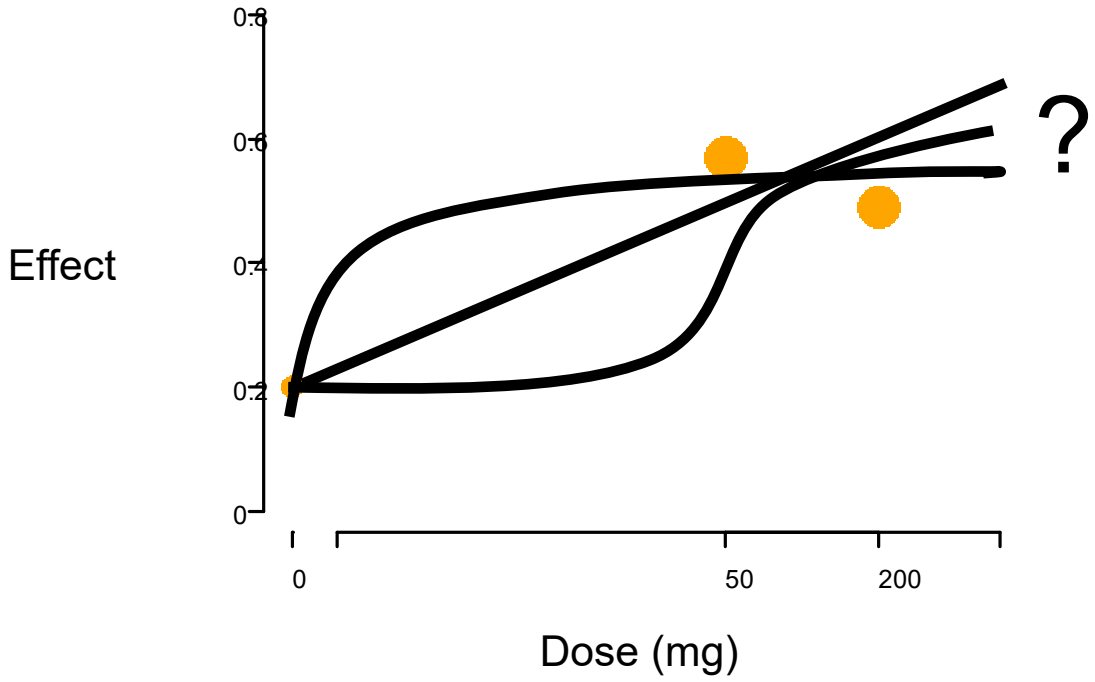
*Adaptive **dose escalation***

- Mainly used in early Oncology studies with high toxicity
- Goals:
  - Estimate the Maximum Tolerated Dose (MTD)
  - Minimize patient exposure to toxic doses
- Traditional algorithmic designs (e.g. «3+3 rule») have given way to designs with better properties
- Continual Reassessment Method (O'Quigley et al. 1990)
- Bayesian adaptive dose escalation
  - Cycle between (i) updating a probability model for dose-limiting toxicities, and (ii) allocating the next cohort of patients

What are adaptive designs?

*Adaptive **dose finding***

- Find minimum effective dose (MED) – but where to look?
- First allocate broadly, then refine the search with additional patients and/or additional doses



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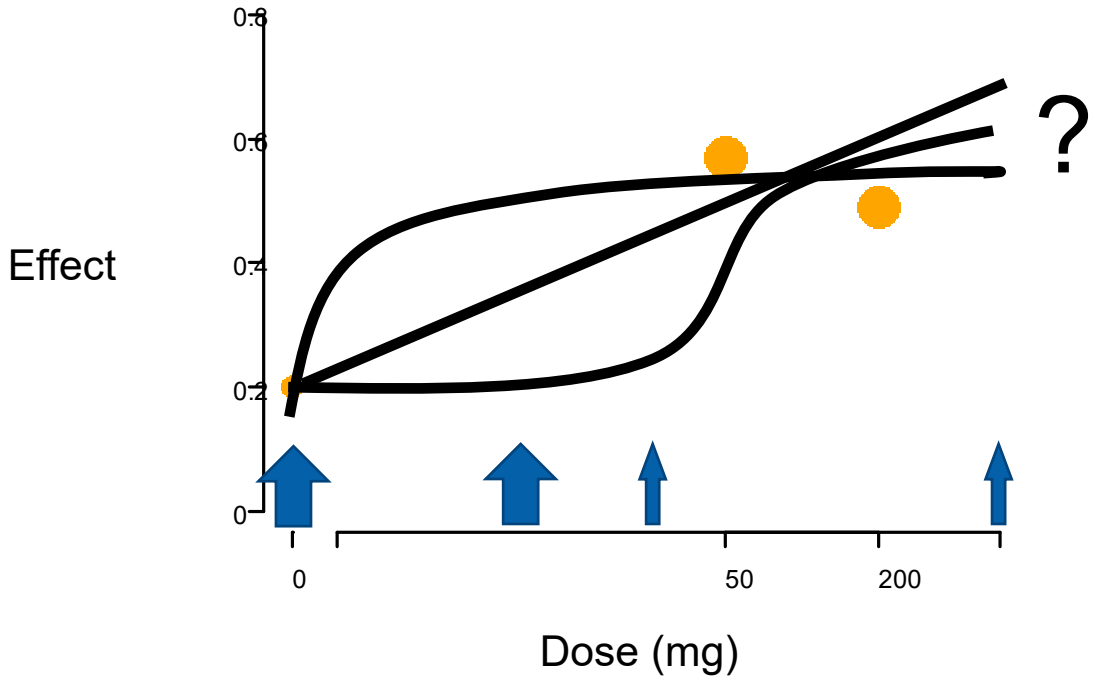

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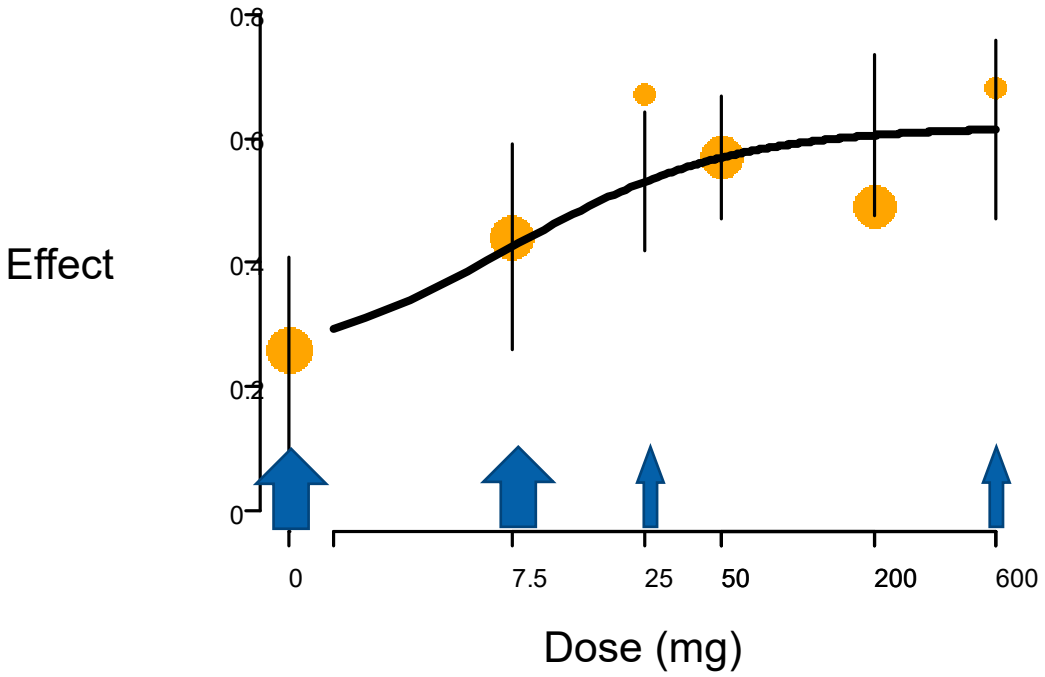


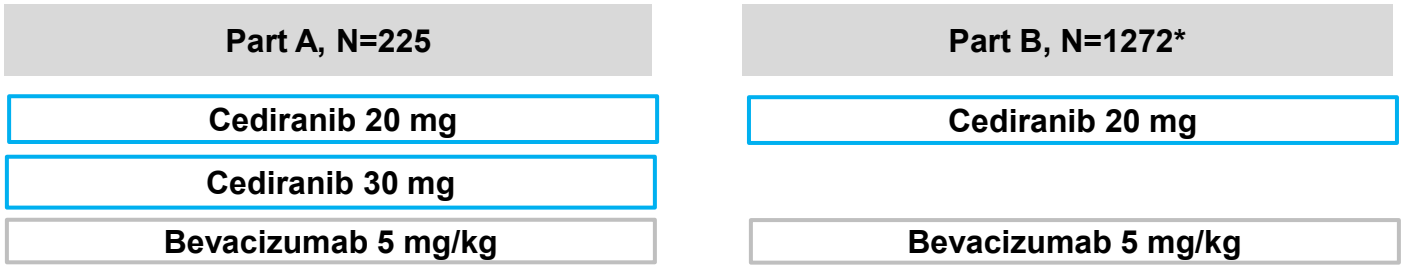
Case study: HORIZON-III

- Pivotal program
  - Cediranib under development for Colorectal Cancer (CRC) (1st line). Promising phase I data and external evidence for Mode of Action argued for start of pivotal program
  - HORIZON-II: Conventional phase III for superiority vs. Placebo (1st line)
  - HORIZON-III: Seamless phase II/III for noninferiority vs. bevacizumab (Standard of Care) (1st line)
  - HORIZON-I: Phase II vs. bevacizumab (*2nd line, started earlier, faster event rate*)
  - All plus chemotherapy, with same 2 active doses and Progression-free Survival (PFS) as primary endpoint

Schmoll et al. (2012); Cuffe et al. (2014)

Case study: HORIZON-III

- HORIZON-III
  - Seamless phase II/III for noninferiority vs. bevacizumab (1st line)



  - At the time of the Interim Analysis (IA), Data Monitoring Committee (DMC) to select 1 dose
    - Based on IA of HORIZON-III (sponsor blinded) *plus final HORIZON-I results (open)*
    - Using predefined criteria for PFS and Response Rate (RR)
  - At the final analysis, test noninferiority of the selected dose vs. bevacizumab based on PFS, using both stages and controlling the overall Type I error

* Plus N=117 recruited to cediranib 30 mg during the IA

Case study: HORIZON-III

- Results (cediranib 20 mg and 30 mg vs. bevacizumab)
  - HORIZON-I
    - Hazard ratio (95% CI): 1.28 (0.85 - 1.95) and 1.17 (0.77 - 1.70)
  - HORIZON-III
    - 20 mg showed greater RR than bevacizumab at the IA and was selected for Part B
    - Hazard ratio at final analysis 1.10 (0.97 - **1.25**); **noninf. margin: 1.20**
    - The effect had **shrunk**, compared to that observed at the IA.
  - HORIZON-I revealed tolerability issues with cediranib. In HORIZON-III, these were often wrongly contributed to chemotherapy, leading to reduction of chemo dose in the cediranib arms, particularly in centers that only participated in Part B. This can have contributed to the shrinking treatment effect.

Case study: HORIZON-III

- Lessons
  - A shrinking treatment effect from phase II to phase III is common even if all conditions (population etc.) remain equal: regression to the mean. But it is of particular concern in a «lean» program where little data is available to corroborate interim findings.
  - Condensation of development program across Phases II and III did not leave time to learn about – or react to – tolerability issues
  - This is an example for the adaptive approach making a development program less flexible
    - It can be risky to pre-specify Phase III before starting Phase II ...!

More complex adaptive designs

- Sources of multiplicity to control for:
  1. Repeated hypothesis testing at IAs → group sequential methods
  2. Adaptations of trial design features → adaptive design methods
  3. Dealing with multiple hypotheses → multiple comparison methods
  - All three sources can be combined!
- Item 3 often requires the closed testing principle
  - Allows treatment arm selection or subgroup enrichment

→ *Next part of this training...*

Marcus, Peritz, Gabriel (1976)