Introduction: Adaptive trials & sample size re-calculation

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Part of the BBS training: ***Advanced group-sequential and adaptive confirmatory clinical trial designs***
Basel, 13 Sep 2022

Learning objectives

Participants should understand:

- What are adaptive clinical trials
  - Major subtypes, distinctions, definitions
- Essential statistical methodology of adaptive trials
  - p-value combinations
  - conditional error functions
  - CRP principle
  - Conditional power and sample size adjustment

What are adaptive designs?

- There are many different types of adaptive trial designs
  - (Group sequential designs, early stopping)
  - Adaptive randomization
  - Adaptive dose escalation
  - Adaptive dose finding
  - Sample size re-estimation
  - Treatment arm selection
  - Enrichment designs
  - ...
- Various «schools» of adaptive designs have developed in parallel, depending on the application area

What are adaptive designs?

Key distinctions:	Our focus:
Exploratory or confirmatory?	→ Confirmatory
Adaptations of which trial features?	→ Any
Using unblinded data?	→ Yes*
Predetermined adaptations or ad-hoc?	→ Both
Based on interim data or external information?	→ Both

- Excluded here:
  - Blinded design modifications (e.g. blinded sample size re-estimation; generally not controversial)
  - Bayesian designs (frequent in early development phases)
  - Response-adaptive randomization
- Our focus:
  - Frequentist confirmatory adaptive designs

* But possibly sponsor-blind

Vandemeulebroecke (2008)

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- FDA draft guidance, 2010: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, 2018); 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.
- **Quiz**: What is the maximal Type I error for a two-stage group-sequ. test with nominal level 5%* if n_2 is chosen in light of the observed first stage effect?
    - 5%? 8.2%? 11.5%?

* Note: I use one-sided tests and p-values unless otherwise specified. Proschan, Hunsberger (1995)

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?

Bauer (1989)

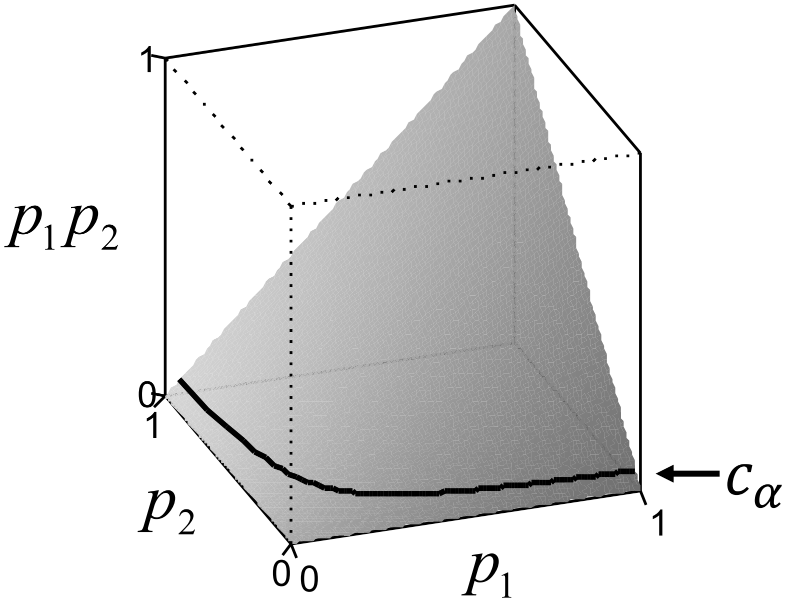
Fisher's product test

- $p_1, p_2 \sim_{H_0} U[0,1]$ 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)

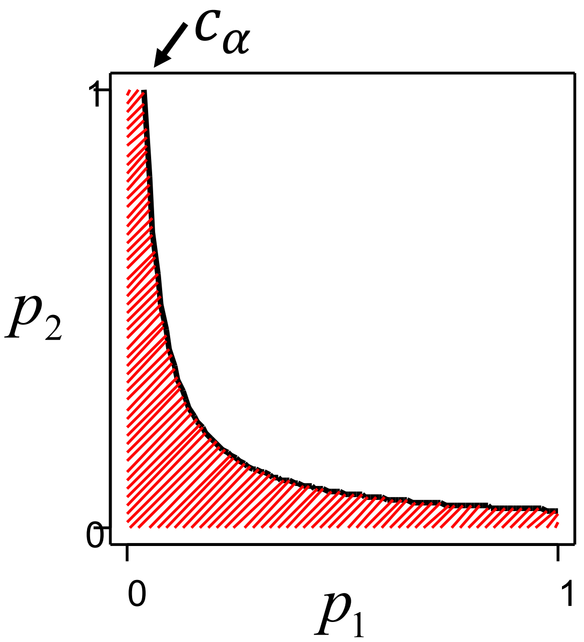
Let’s look at it geometrically

- p-value combination



Reject if $p_1 p_2 \leq c_\alpha$

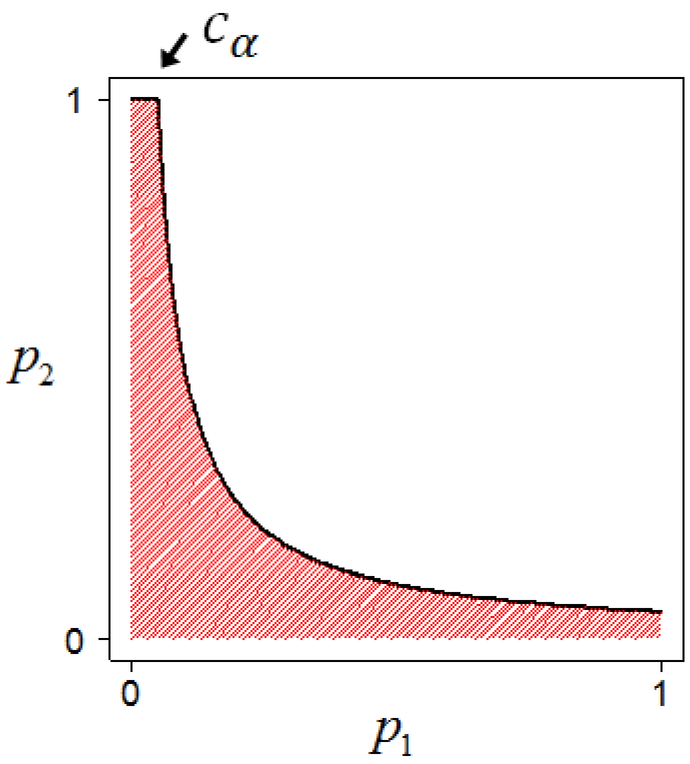
- Projection onto the plane



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

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

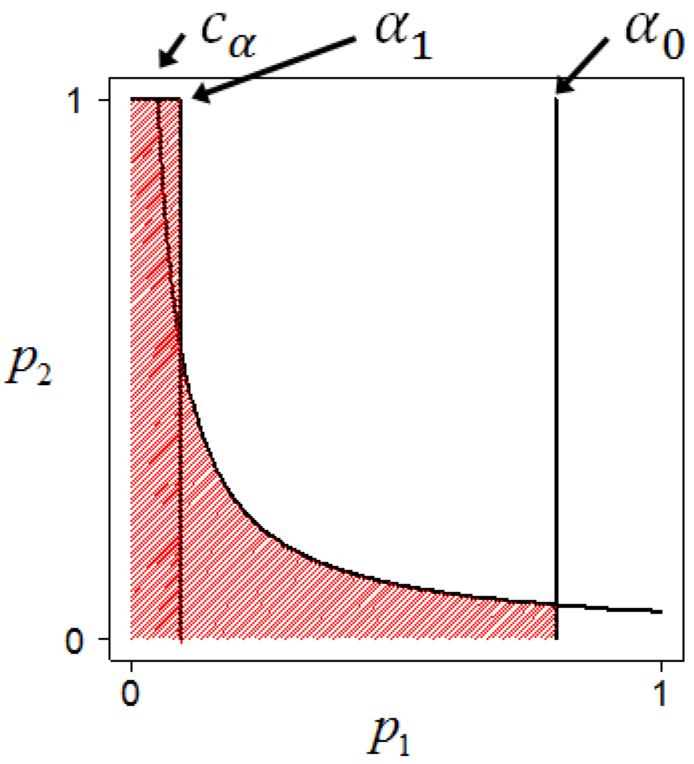
The conditional error function



- 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).

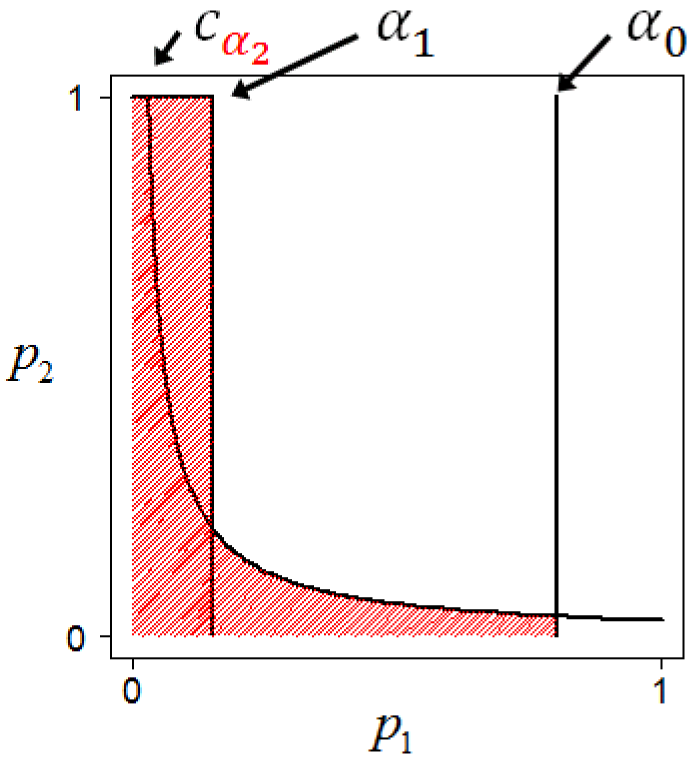
Early stopping



- 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

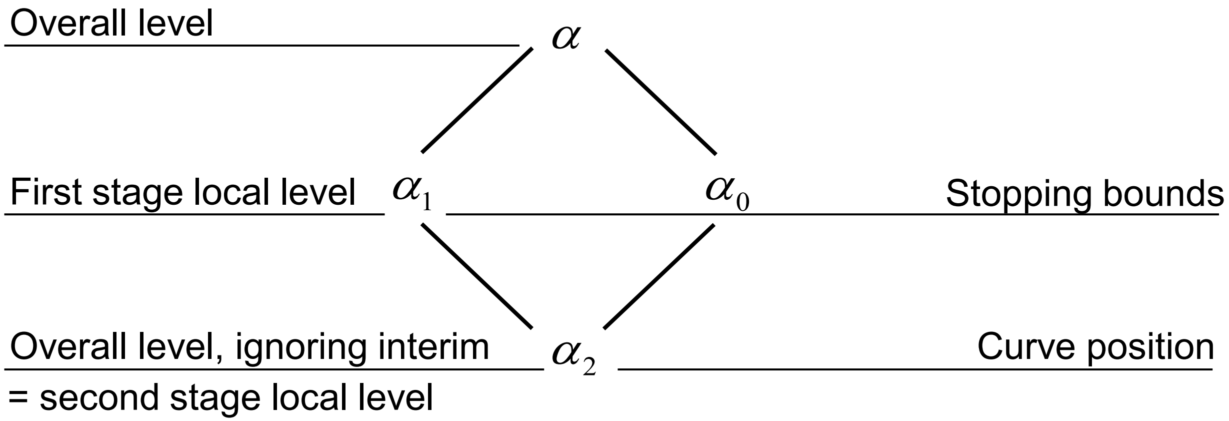


- Reject after second stage if $p_2 \leq c_{\alpha_2}/p_1$
  - This uses a different c.e.f. of the same family
  - The final test is performed at the local level α_2
- Red area must remain α $\alpha_1 + c_{\alpha_2}\big(\ln(\alpha_0) - \ln(\alpha_1)\big) = \alpha$

Bauer, Röhmel (1995)

The «alpha calculus»

- Four parameters are interdependent



Overall level α

First stage local level α_1

α_0 Stopping bounds

Overall level, ignoring interim α_2

= second stage local level

Curve position

- 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?

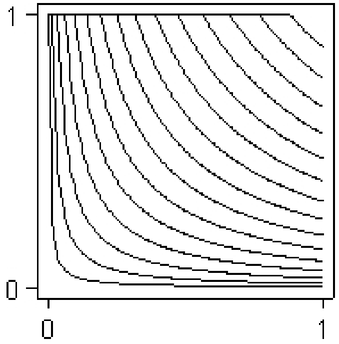
Vandemeulebroecke (2006)

Inverse normal method & more

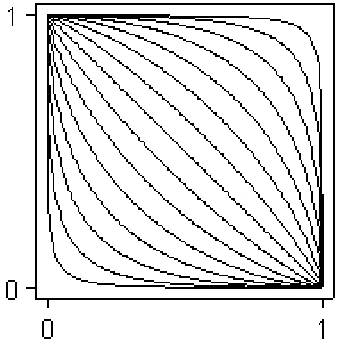
- Another natural way to combine p-values:

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

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



Product test

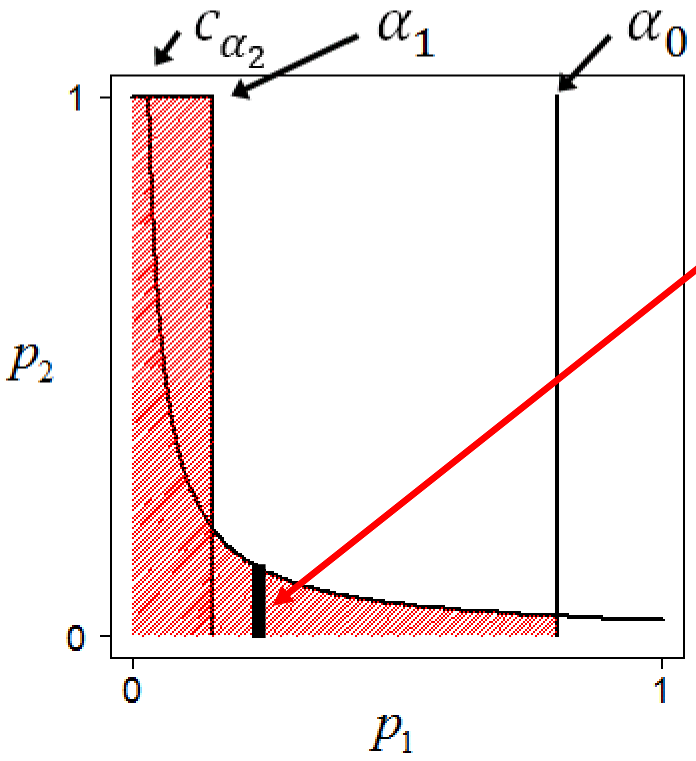


Inverse normal method (INM)

- 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 $P_{H_0}(p_2 \leq u \mid p_1) \leq u$ 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); $i = 1, \dots, n_k$; 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); $i = 1, \ldots, n_k$
  - $n = n_1 + n_2$ total sample size per arm
  - Denote $\vartheta = \frac{\mu - \nu}{\sigma}$

→ *Next slide*

Proschan, Hunsberger (1995)

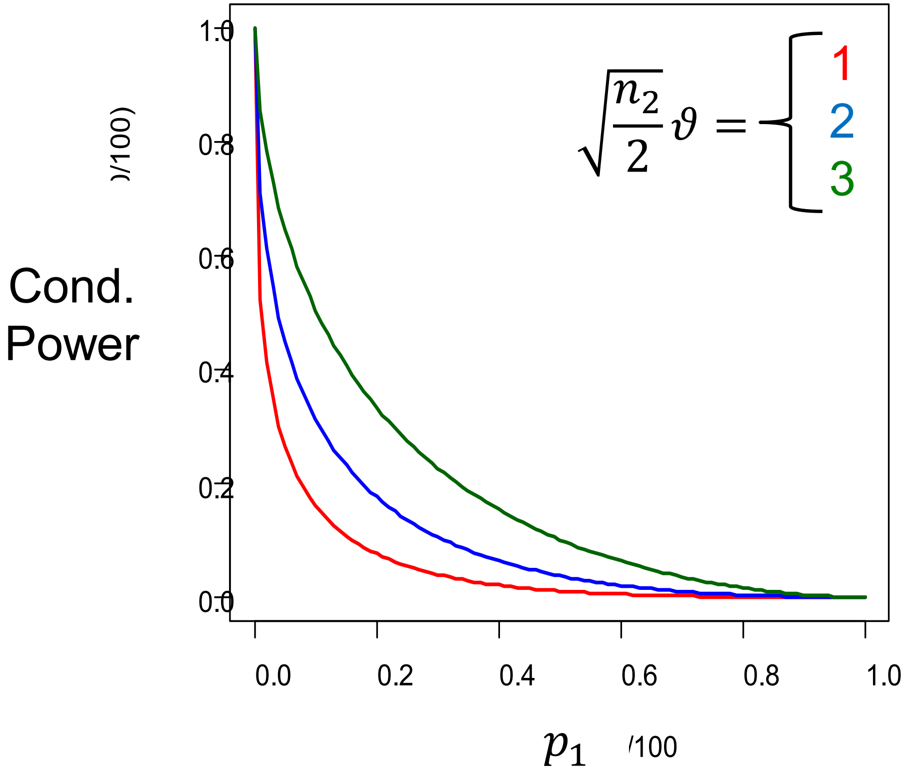
Conditional power

- $$\begin{aligned} CP_{\vartheta} &= P_{\vartheta}\left(\frac{1}{\sqrt{2}}\left(\Phi^{-1}(1-p_1)+\Phi^{-1}(1-p_2)\right) \geq u_{\alpha} \,\middle|\, p_1\right) \\ &= P_{\vartheta}\left(\frac{1}{\sqrt{2}}(Z_1+Z_2) \geq u_{\alpha} \,\middle|\, Z_1 = z_1\right) \\ &= P_{\vartheta}\left(Z_2 \geq \sqrt{2}u_{\alpha} - z_1\right) \\ &= P_{\vartheta}\left(Z_2 - \sqrt{\frac{n_2}{2}}\vartheta \geq \sqrt{2}u_{\alpha} - z_1 - \sqrt{\frac{n_2}{2}}\vartheta\right) \\ &= 1 - \Phi\left(\sqrt{2}u_{\alpha} - z_1 - \sqrt{\frac{n_2}{2}}\vartheta\right) \end{aligned}$$

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

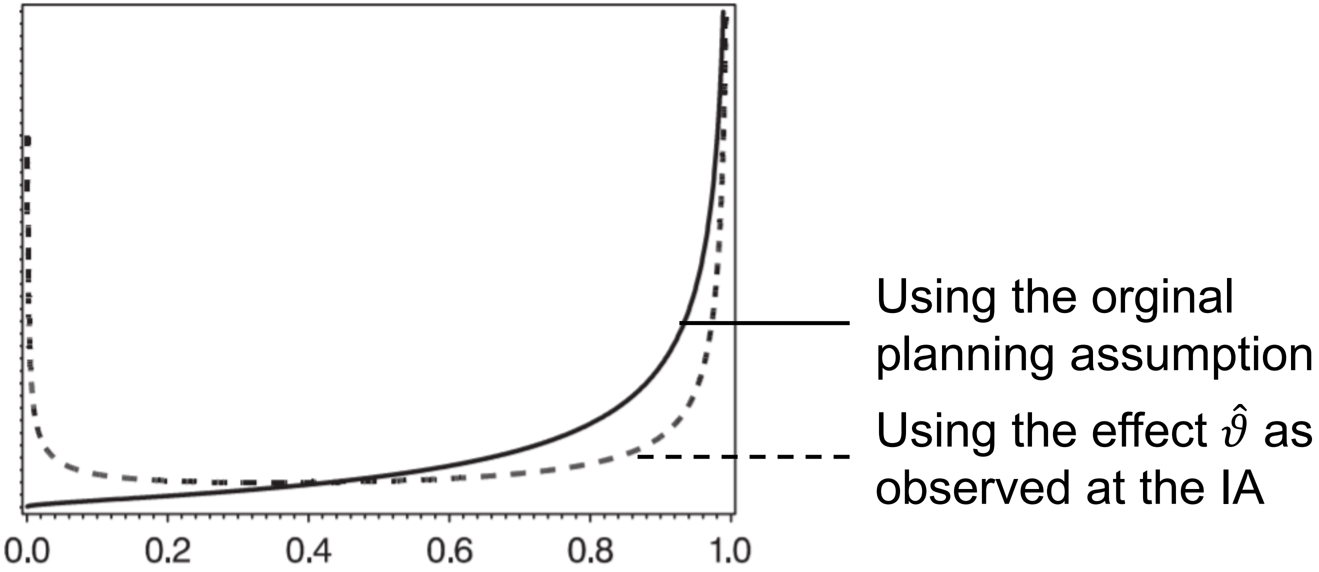
    Conduct the second stage and perform the final inference as planned through the adaptive design
- **Quiz**: What ϑ would you use in CP_ϑ?

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)

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»

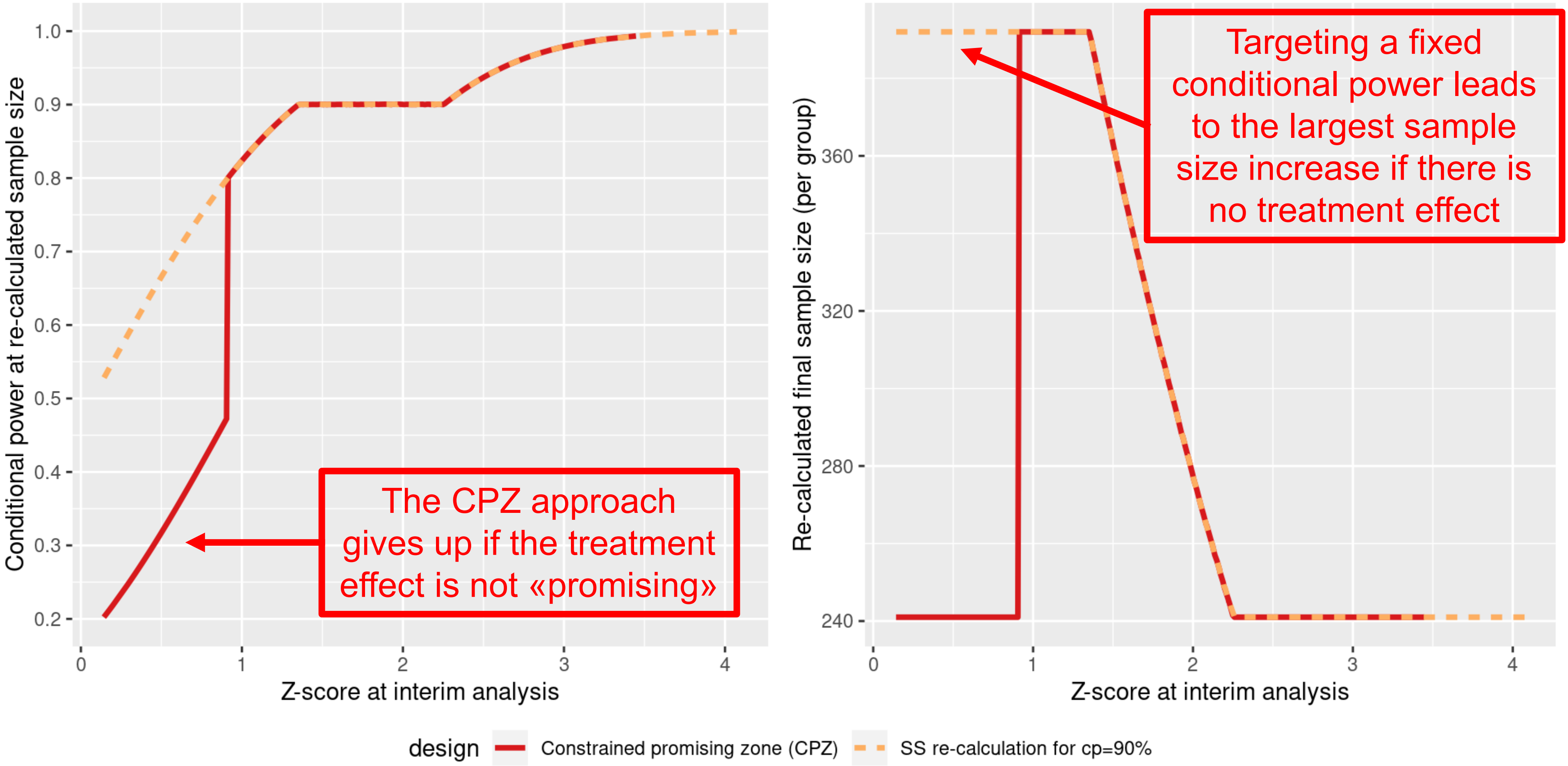
Hsiao et al., 2019. Credit to Marcel Wolbers and Kaspar Rufibach

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

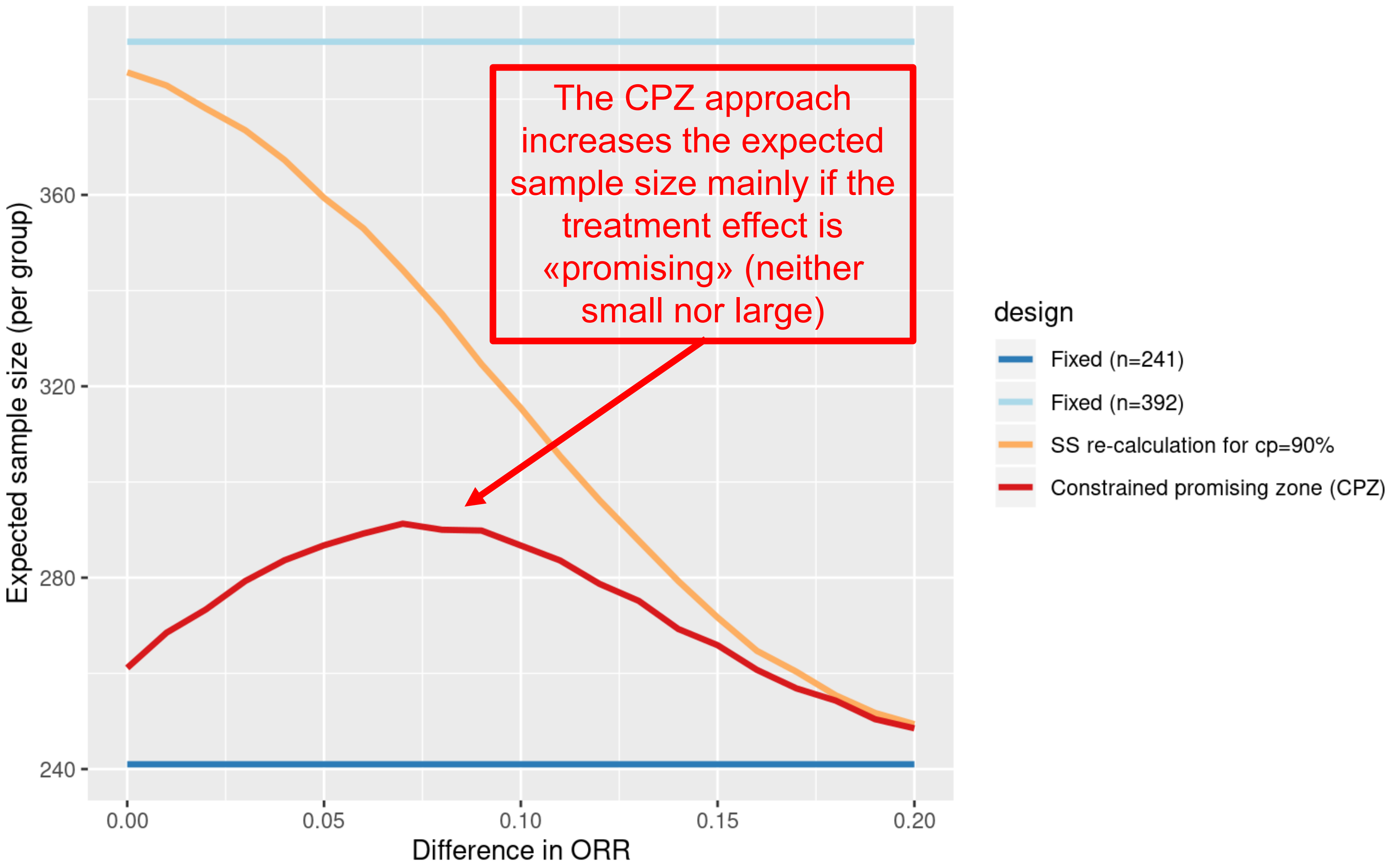


The CPZ approach gives up if the treatment effect is not «promising»

Targeting a fixed conditional power leads to the largest sample size increase if there is no treatment effect

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

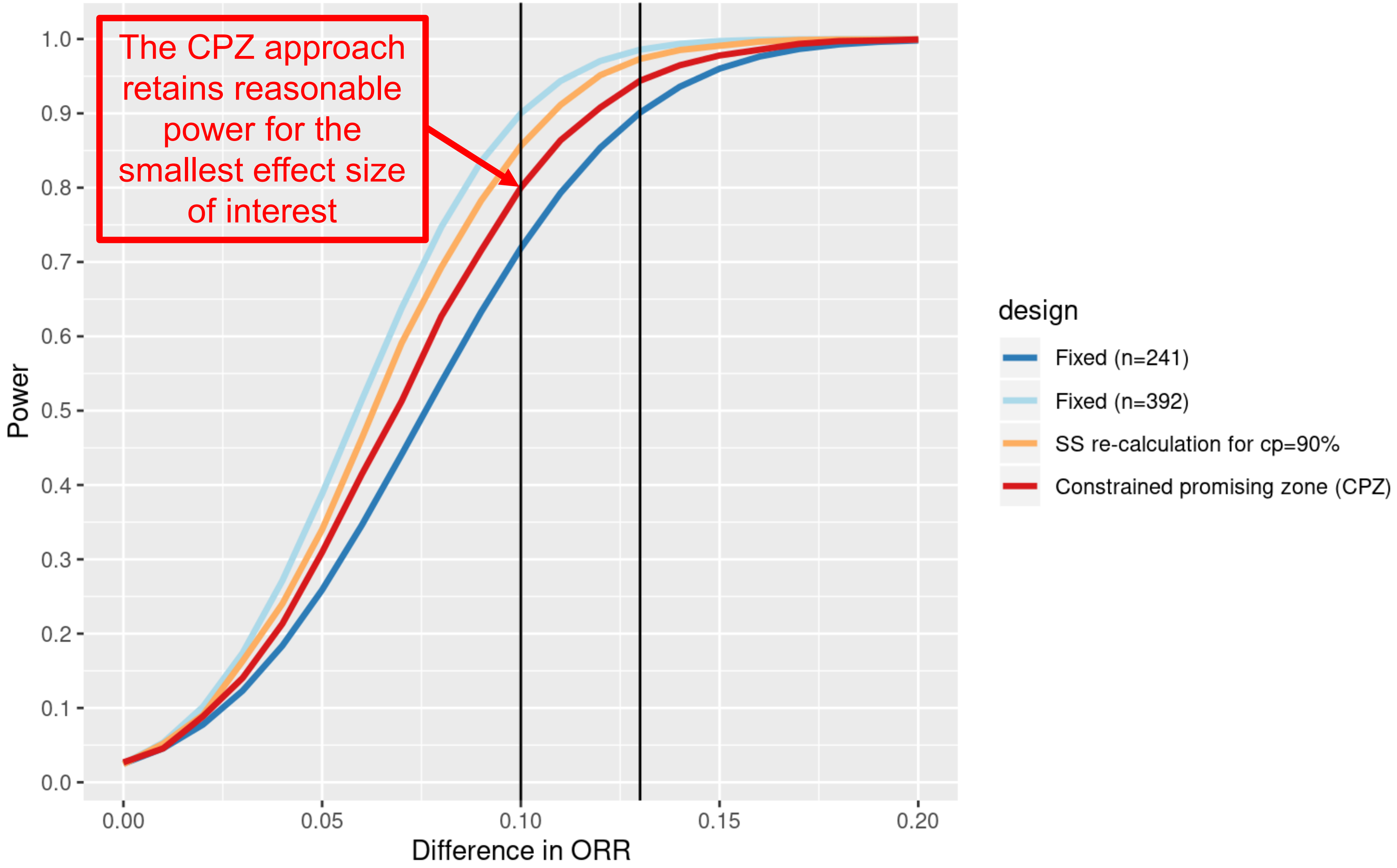
Expected sample size depending on effect size



The CPZ approach increases the expected sample size mainly if the treatment effect is «promising» (neither small nor large)

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

Power depending on effect size



The CPZ approach retains reasonable power for the smallest effect size of interest

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

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 literature of such designs versus «more efficient» group-sequential designs
  - E.g., Liu et al, 2018: «*...under reasonable decision rules for increasing sample size […] there is little or no loss of efficiency for the adaptive designs in terms of unconditional power. The two approaches, however, have very different conditional power profiles.*»
- 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!**

References (1)

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- EastAdapt and EastSurv: http://www.cytel.com/software/east

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- 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/