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Adaptive dose-finding with power control

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Dose-finding case study

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- Design of Phase II trial for new drug

- **Treatment effect θ of drug is uncertain** (also, some risk of no effect at all …)
- Desire to investigate dose-response curve (i.e. **investigate several doses**), but limited resources

Outline

- Sample size recalculation
  - A quick review
  - Usefulness and problems with it
- Dose-finding case study
  - Application of sample size recalculation
  - Adaptive design

Sample size recalculation

- Sample size in two sample case for testing null hyp. $\mathbf{H_0: \theta=0}$ (no treatment effect) vs $\mathbf{H_1: \theta>0}$ (one-sided) with normal assumption (and common variance) is

$$n = \frac{2\sigma^2}{\theta^2}(z_\alpha + z_\beta)^2$$

- Problem:
  - How to choose θ? Guess of true effect?
  - If effect θ large, study can be small
  - Only if effect θ small, larger sample size justified

Sample size recalculation

- Sample size is

$$n = \frac{2\sigma^2}{\theta^2}(z_\alpha + z_\beta)^2$$

- Idea:
  - Calculate initial sample size n_0 based on a guess for θ,
  - perform an interim analysis after $n_1 < n_0$ obs
  - Recalculate n based on interim estimate for θ

Sample size recalculation

- Example for recalculation rule:

$$N = \frac{2\sigma^2}{\hat{\theta}^2_{\text{interim}}}(z_\alpha + z_\beta)^2$$

- In practice, one will use an upper (and lower) bound for the sample size, e.g.

$$N = \begin{cases} n_{\max}, & \text{if } \hat{\theta}_{\text{interim}} < c_{\text{low}} \\ \dfrac{2\sigma^2}{\hat{\theta}^2_{\text{interim}}}(z_\alpha + z_\beta)^2, & \text{if } \hat{\theta}_{\text{interim}} \in (c_{\text{low}}, c_{\text{upp}}) \\ n_{\min}, & \text{if } \hat{\theta}_{\text{interim}} > c_{\text{upp}} \end{cases}$$

Sample size recalculation

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- Sample size recalculation has impact on distribution of Z_{final}. Therefore, the conventional test

  $$\text{reject } H_0 \text{ iff } Z_{final} > z_{alpha}$$

  might not control the alpha level.
- In practically relevant situations, type I error can be considerably higher than alpha (e.g. = 0.07 instead of alpha=0.05, Shun *et al*, 2001)

Sample size recalculation

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- Instead of using the conventional test

  reject H_0 iff $Z_{final} > z_{alpha,}$

  other tests can be used to control the type I error (e.g. Cui *et al*, 1999; Lehmacher & Wassmer, 1999) weighting observations before and after interim analysis differently
- However, it **would simplify communication in practice, if conventional test could be used** in a specific situation **with type I error control**

Sample size recalculation

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- The flexible sample size can be an administrative problem
  - Planning of trial logistics more difficult
  - Especially regulatory perspective fears: back-calculation or guessing of interim effect estimate

❖ On the other hand, sample size recalculation has advantage of better power control

Dose-finding case study

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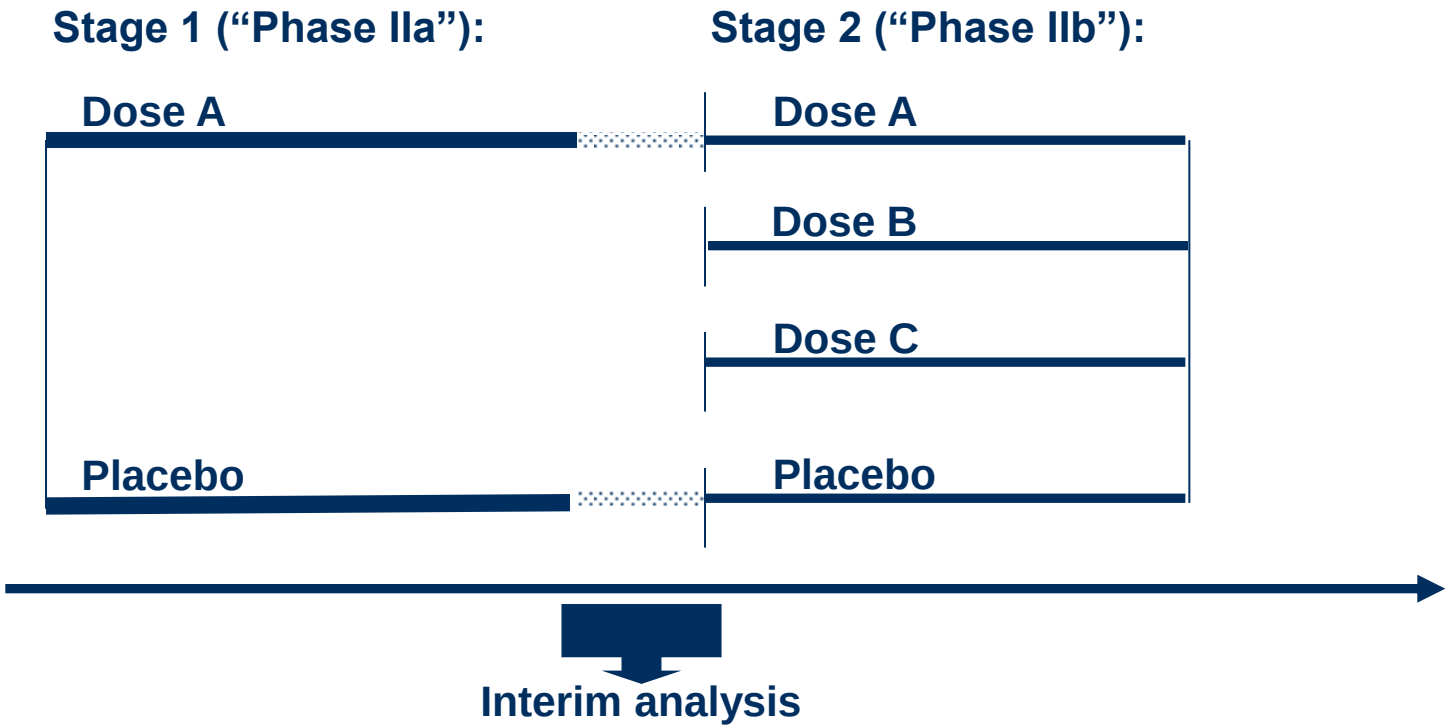
- Design of Phase II trial for new drug

- **Treatment effect θ of drug is uncertain** (also, some risk for no effect at all …)
- Desire to investigate dose-response curve (i.e. **investigate several doses**), but limited resources

Dose-finding case study

- Basic idea: "Seamless Phase II a/b design"

Proof that the drug works Dose finding



Dose-finding case study

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- Investment in dose-finding part should be justified by some evidence of drug effect

- Only justified to run the Phase IIb part if the chance of success is considerably high

- So: require certain conditional power $1-\gamma$ of success for final analysis before going into Phase IIb part, e.g. $1-\gamma=0.7$.

Conditional power

- Conditional power of success of the total study (see e.g. Jennison & Turnbull, 2000, Section 10.1, 10.2 incl. historical background):
  - $\text{Cond.power}(\theta, \text{interim data}) = P_\theta(\text{rej. } H_0 \text{ at final ana.} \mid \text{interim data})$
  - For N(θ,σ²)-distributed observations, the conditional power is

$$\Phi\left(\frac{z_{\text{interim}}\sqrt{n_1/(2\sigma^2)} - z_\alpha\sqrt{(n_1+n_2)/(2\sigma^2)} + \theta n_2/(2\sigma^2)}{\sqrt{n_2/(n_1+n_2)}}\right)$$

Conditional power at observed θ

- Conditional power $\text{Cond.power}(\hat{\theta}_{\text{interim}}, \text{interim data})$ for success of the total study at the observed θ is then for N(θ,σ²)-distributed observations:

$$\Phi\left(\frac{z_{\text{interim}} / \sqrt{n_1/(n_1+n_2)} - z_\alpha}{\sqrt{n_2/(n_1+n_2)}}\right)$$

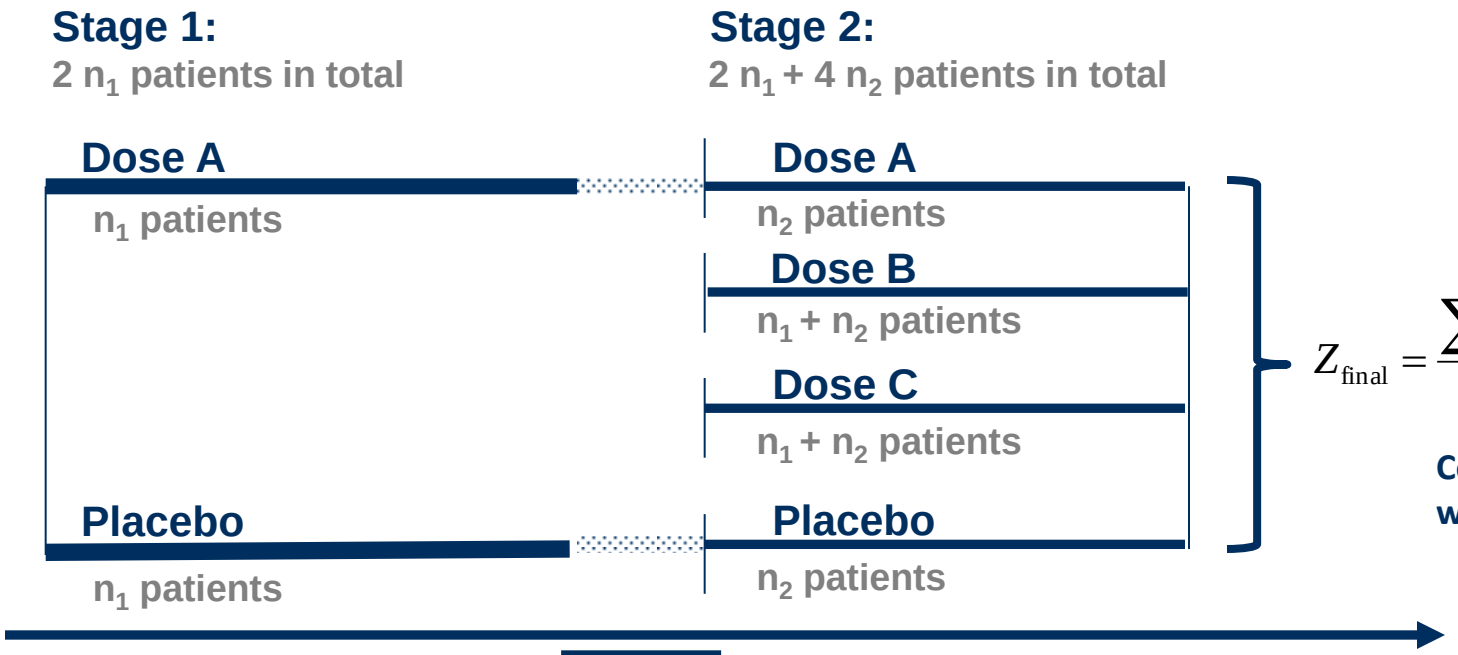
Predictive power

- Predictive power (see e.g. Jennison & Turnbull, 2000, Section 10.3):
  - $\text{Pred.power}(\theta, \text{interim data})$

    $= \int \text{Cond.power}(\theta, \text{interim data}) \pi(\theta \mid \text{interim data}) d\theta$

    Likelihood for Stage 1 obs.
  - For N(θ,σ²)-distributed observations, the predictive power is

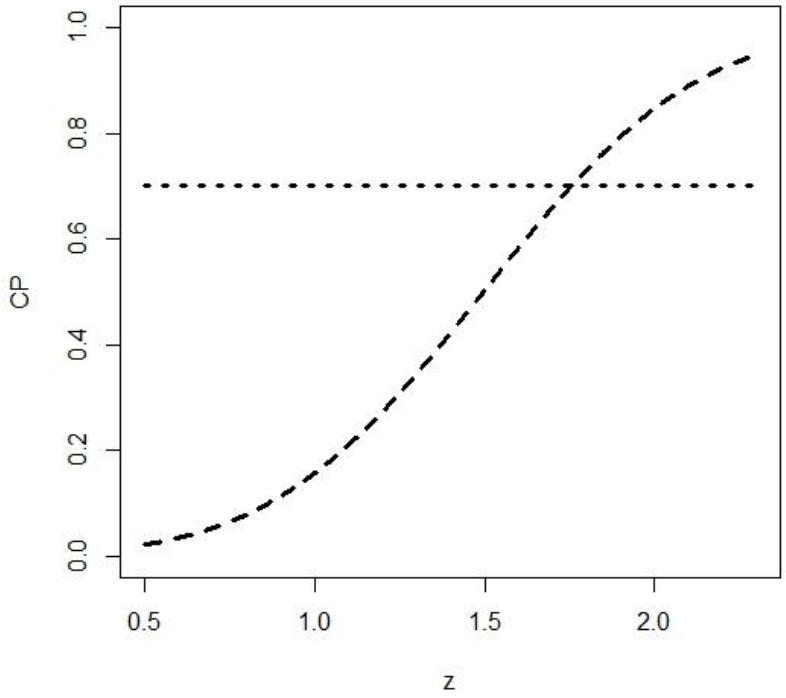
$$\Phi\left(\frac{z_{\text{interim}} - z_{\alpha}\sqrt{n_1/(n_1+n_2)}}{\sqrt{n_2/(n_1+n_2)}} \right)$$



$$Z_{\text{interim}} = \frac{\sum_{i=1}^{n_1}(X_{1i} - X_{0i})}{\sqrt{2\sigma^2 n_1}}$$

Decision rule for going to Phase IIb

- CP vs $z_{interim}$



Example for alpha=0.025, (i.e. $z_\alpha = 1.96$), $n_1/(n_1+n_2)=7/12$

- So, stop for futility if $z_{interim}<1.76$ to ensure a conditional power of $1-\gamma=0.7$?
- Hurdle might be too high…

Decision rule for going to Phase IIb

- Conditional power below target of 1-γ=0.7 means:
    - Treatment effect seems lower than anticipated
- Increasing the sample size increases conditional power
- On the other hand, if treatment effect is lower than anticipated, it might be less relevant to study smaller doses

- Therefore:
  If CP too low → drop dose C, or dose B and C, and distribute the patients instead on remaining doses

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Stage 1:

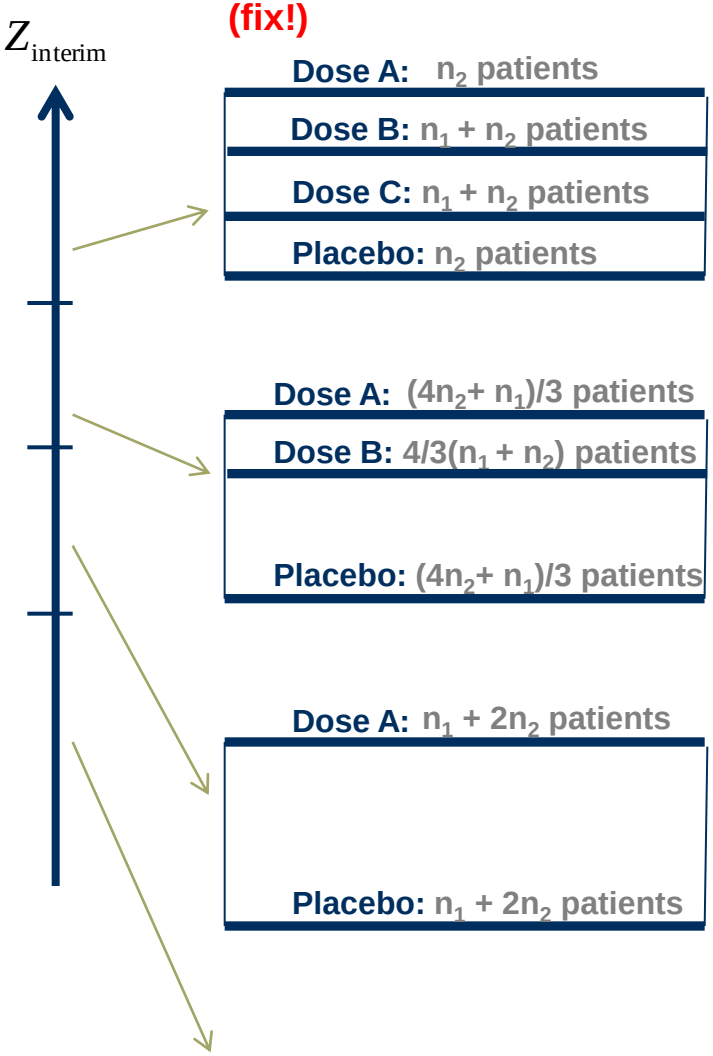
2 n_1 patients in total

Dose A

n_1 patients

Placebo

n_1 patients



Stage 2:

2 n_1 + 4 n_2 patients in total (fix!)

Dose A: n_2 patients
Dose B: $n_1 + n_2$ patients
Dose C: $n_1 + n_2$ patients
Placebo: n_2 patients

Dose A: $(4n_2 + n_1)/3$ patients
Dose B: $4/3(n_1 + n_2)$ patients
Placebo: $(4n_2 + n_1)/3$ patients

Dose A: $n_1 + 2n_2$ patients
Placebo: $n_1 + 2n_2$ patients

Stop for futility

Compare dose A with placebo:

$$Z_{final} = \frac{\sum_{i=1}^{n}(X_{1i} - X_{0i})}{\sqrt{2\sigma^2 n}}$$

$$n = \begin{cases} n_1 + n_2, \\ 4/3(n_1 + n_2), \\ 2(n_1 + n_2), \\ n_1 \end{cases}$$

Sample size n for primary test at final analysis is adaptive (i.e. sample size recalculation)

Sample size recalculation

- We would like to use the conventional test

  reject H_0 iff $Z_{final} > z_{alpha}$.
- Mehta & Pocock (2011) point out that in certain important cases, type I error controlled with conventional test above
- Broberg (2013) has provided explicit bounds for when the type I error is at most alpha for the conventional test:
- Sample size n_1+n_2 can be raised to $(n_1+n_2)V$, $V>1$, based on observed z-value $z_{interim}$ in interim, if

$$z_{\text{interim}} > z_{\alpha}\frac{1}{\sqrt{\tau}}\frac{\sqrt{V-\tau}-\sqrt{V-V\tau}}{\sqrt{V-\tau}-\sqrt{1-\tau}}$$

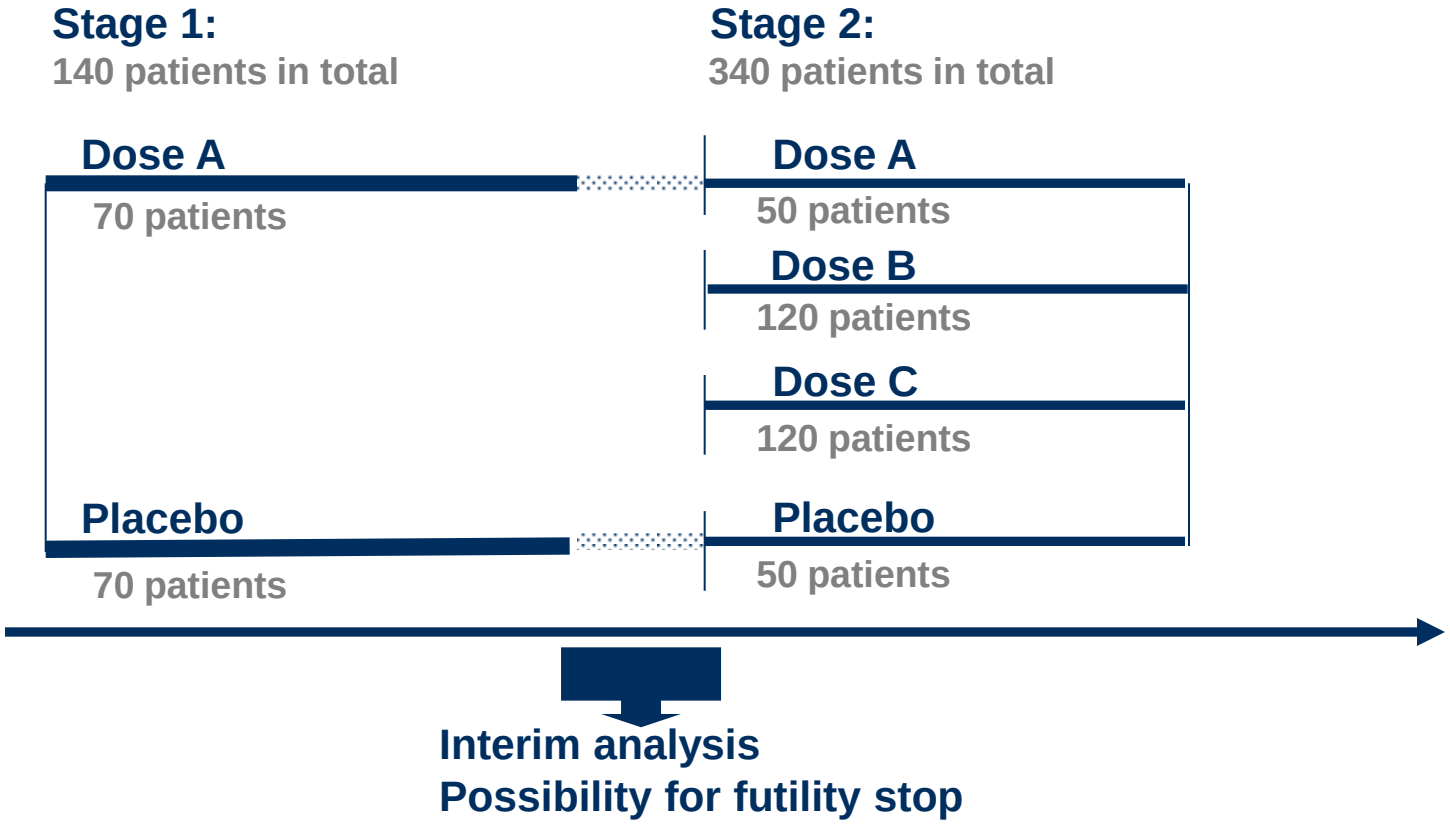
  where $\tau=n_1/(n_1+n_2)$.

Sample size recalculation

- In our situation, we raise sample size from n_1+n_2 to $4/3(n_1+n_2)$ or to $2(n_1+n_2)$. This is allowed in combination with not changing the final test if:

$$z_{\text{interim}} > z_\alpha \frac{1}{\sqrt{\tau}} \frac{\sqrt{4/3-\tau}-\sqrt{4/3-4\tau/3}}{\sqrt{4/3-\tau}-\sqrt{1-\tau}}$$

$$z_{\text{interim}} > z_\alpha \frac{1}{\sqrt{\tau}} \frac{\sqrt{2-\tau}-\sqrt{2-2\tau}}{\sqrt{2-\tau}-\sqrt{1-\tau}}$$


Stage 1:
140 patients in total
Stage 2:
340 patients in total
Dose A
70 patients
Dose A
50 patients
Dose B
120 patients
Dose C
120 patients
Placebo
70 patients
Placebo
50 patients
Interim analysis
Possibility for futility stop

Sample size recalculation

- In our situation, we raise sample size from n_1+n_2 to $4/3(n_1+n_2)$ or to $2(n_1+n_2)$. This is allowed in combination with not changing the final test if:

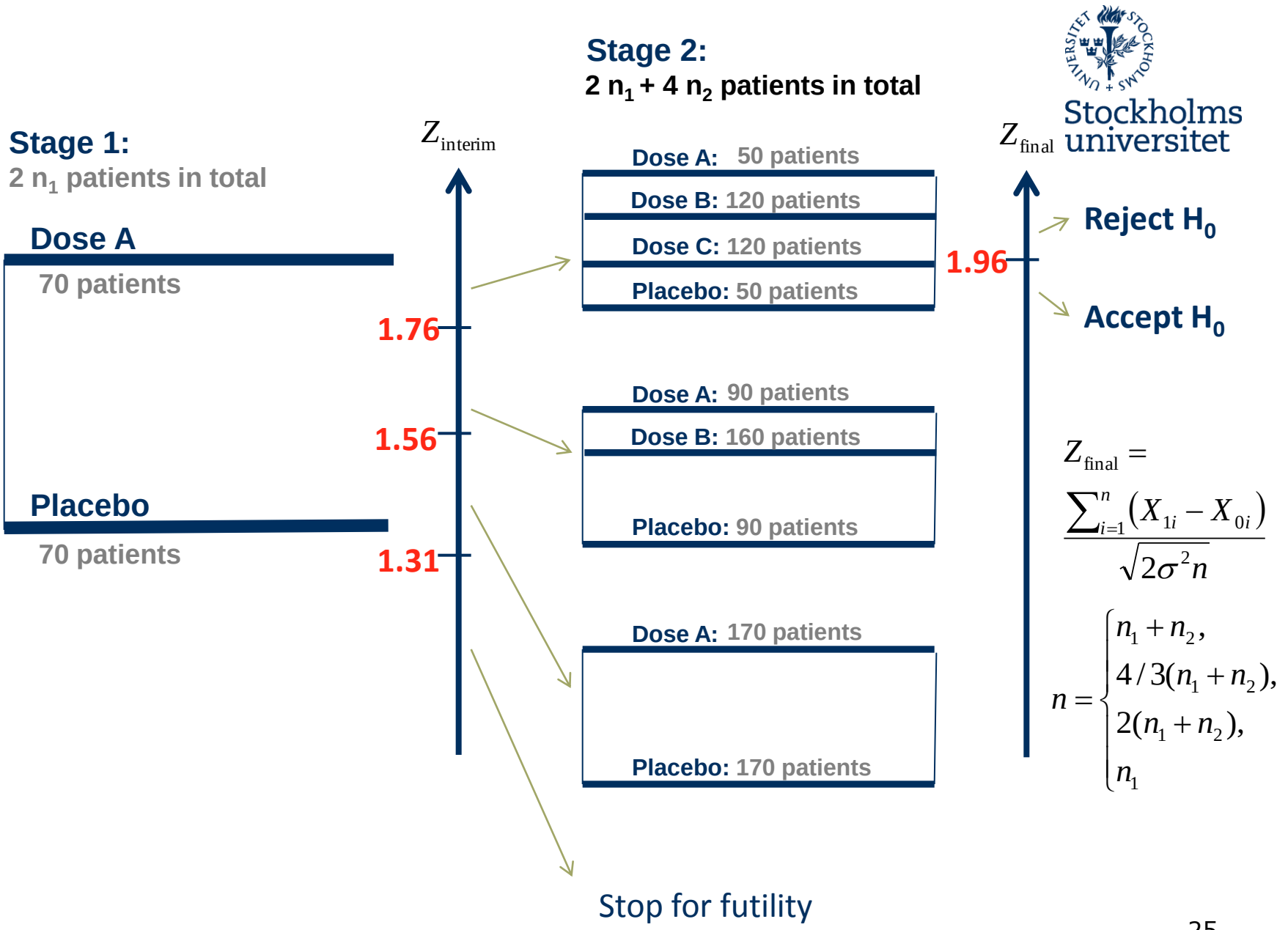
$$z_{\text{interim}} > z_\alpha \frac{1}{\sqrt{\tau}} \frac{\sqrt{4/3-\tau}-\sqrt{4/3-4\tau/3}}{\sqrt{4/3-\tau}-\sqrt{1-\tau}} = 1.40$$

$$z_{\text{interim}} > z_\alpha \frac{1}{\sqrt{\tau}} \frac{\sqrt{2-\tau}-\sqrt{2-2\tau}}{\sqrt{2-\tau}-\sqrt{1-\tau}} = 1.31$$

(alpha=0.025, $z_\alpha = 1.96$, tau=7/12)

Sample size recalculation

- Aim for keeping conditional power >1-γ (e.g. 0.7)
- This desire implies:
    - Drop dose C and increase sample size to $4/3(n_1+n_2)$ if **$1.56 < z_{interim} <$ 1.76**
    - Drop dose C and B and increase sample size to $2(n_1+n_2)$ if **$1.30 < z_{interim} <$ 1.56**



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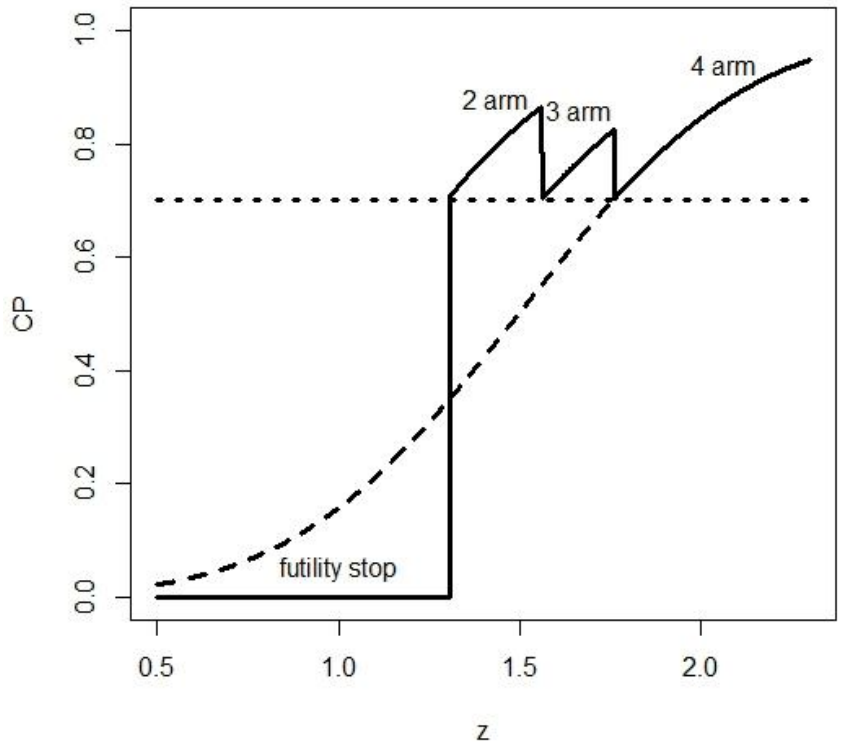
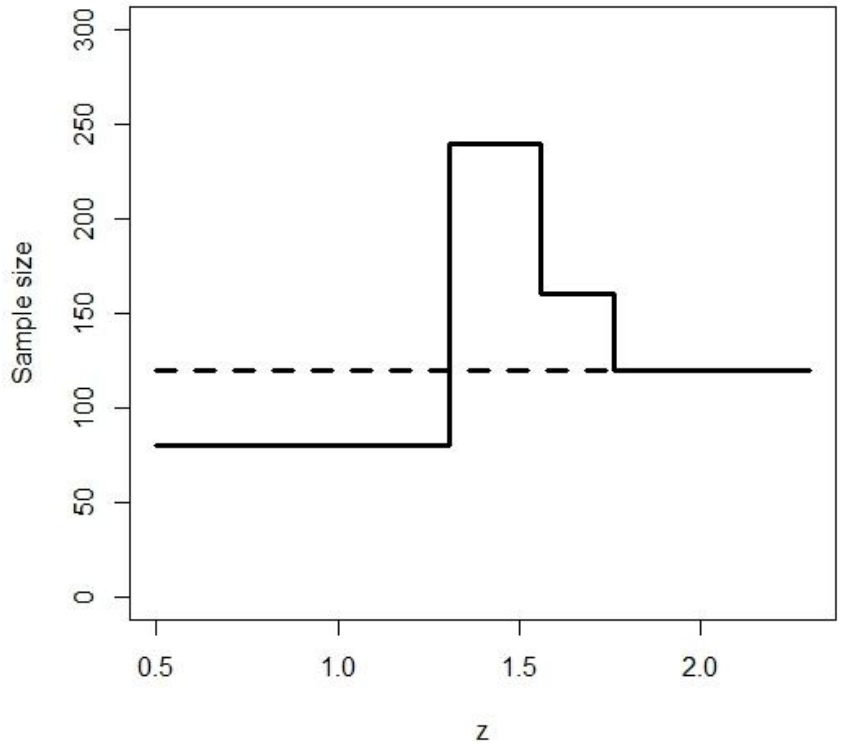
Conditional power of adaptive design

- CP vs $z_{interim}$



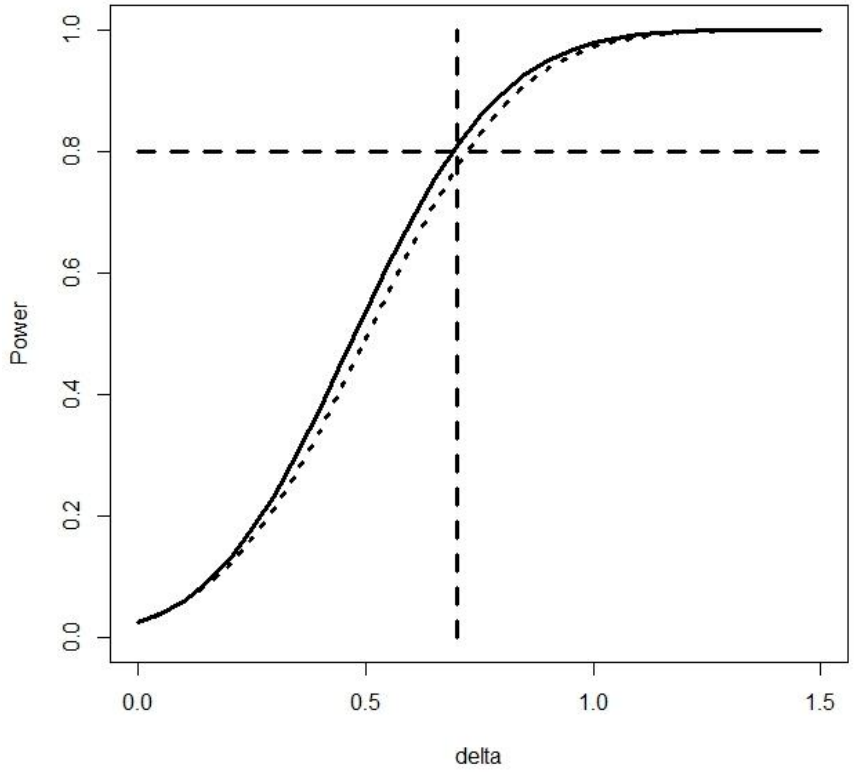
Sample size rule

- Sample size for Dose A and placebo vs $z_{interim}$



Unconditional power

- Power for comparison of Dose A with placebo

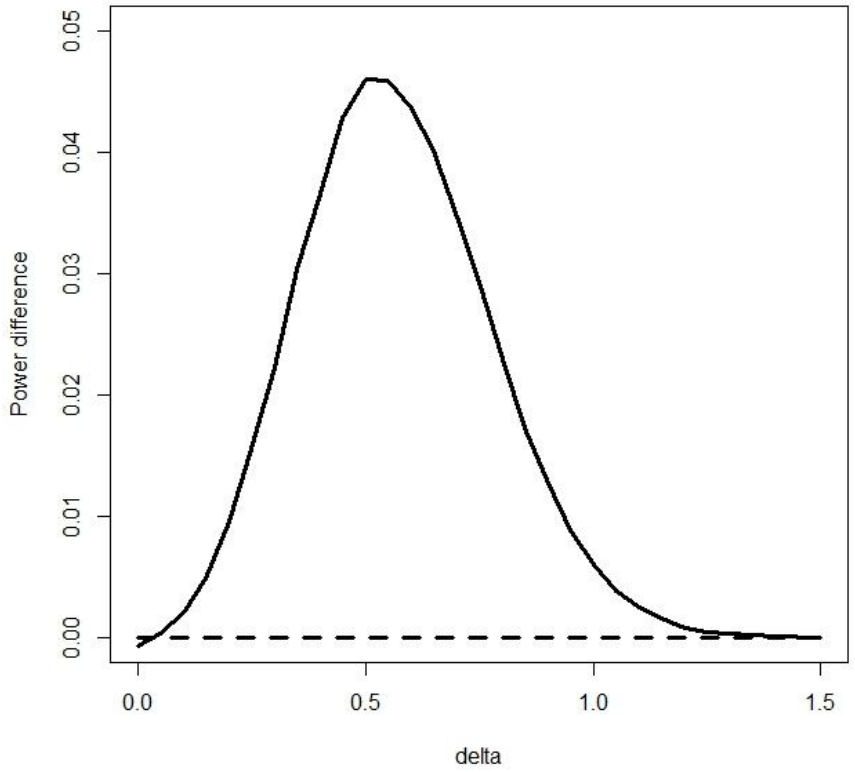


Solid line: Adaptive design

Dotted: Fixed with 120/arm

Unconditional power

- Power for comparison of Dose A with placebo



Power difference

Adaptive design

-

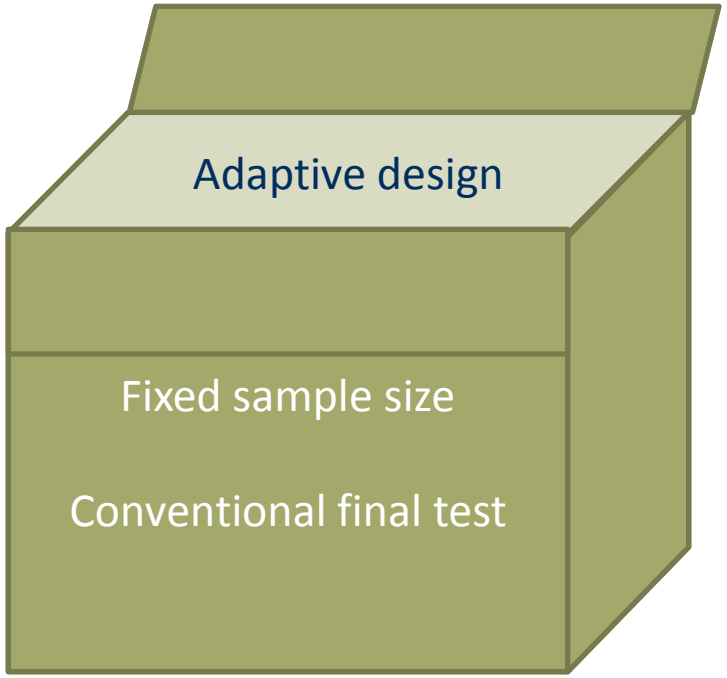
Fixed with 120/arm

Summary

- We can increase the conditional power to a reasonable size in dose-finding trials by **gradually switching the focus from dose-finding to effect proof**
- Some of the important practical limitations of sample size recalculation are avoided
- It is feasible to conduct a trial with this design (see similar two-stage design: Miller *et al*, 2014)

- The logistics are still more complicated compared to a fixed design trial as treatment allocation is adaptive
- Allocation rate to placebo can change during trial

Summary


Adaptive design
Fixed sample size
Conventional final test

References

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Conducted adaptive design