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Adaptive designs: why to use them and some experiences

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MRC | Hubs for Trials Methodology Research

Probability of approval of new drug regimen (Wong et al., 2019)

- phase II: $<40\%$
- phase III: $\sim 60\%$

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Likely causes for failure:

- taking forward futile treatments
- studying the wrong patient population
- poor precision (optimal dose, maximum tolerated dose, safety)

Can we do better?

Adaptive Designs

Idea

Modify an ongoing trial

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by design

based on reviewing accrued data at interim

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based on reviewing accrued data at interim

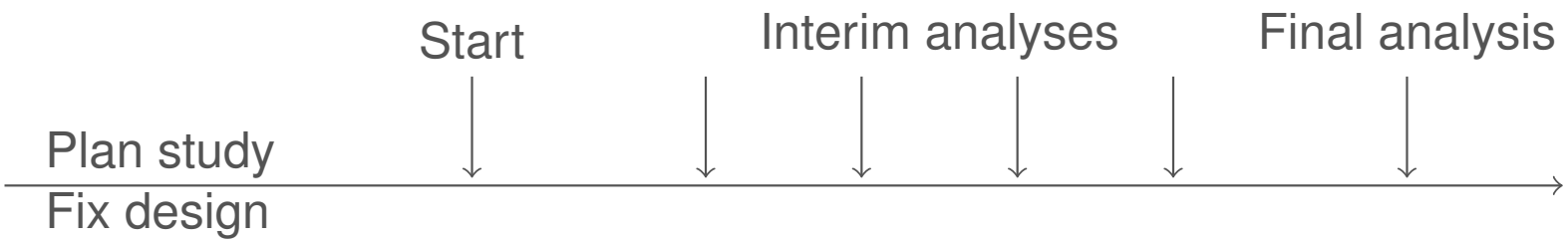
to enhance flexibility

without undermining the study's integrity and validity.

(Chow et al. 2005)

Fixed sample design

Adaptive design



At each interim:

- decide whether or not to stop
- change sample size
- change allocation ratio
- drop or add a dose
- . . .

The TAILoR study

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TAILoR: Telmisartin And Insulin Resistance in HIV.

Ambition: Reduce insulin resistance in HIV patients receiving antiretroviral therapy.

Treatment: Different doses of a licensed drug (in a different therapeutic area). Inappropriate to assume a monotone dose-response relationship.

Endpoint: Change in insulin resistance as measured using HOMA-IR index (baseline - week 12).

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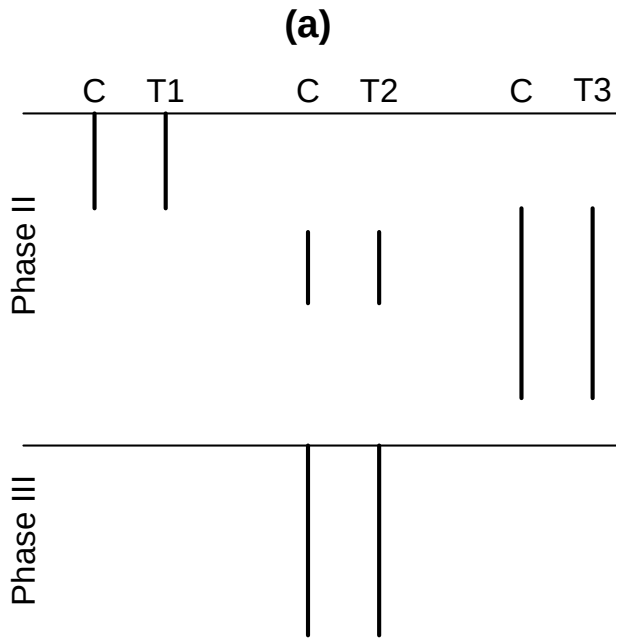
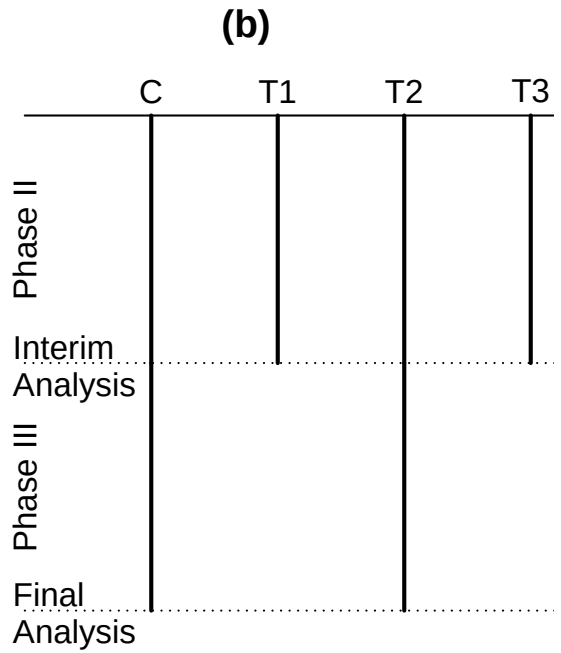
Multi-arm multi-stage trials

- Compare several active treatments against common control
- Select one of more treatment at interim





Testing multiple hypothesis

Responses: $X_{k,i} \sim N(\mu_k, \sigma^2), \quad i = 1, \ldots, n, \, k = 0, 1, \ldots, 4$

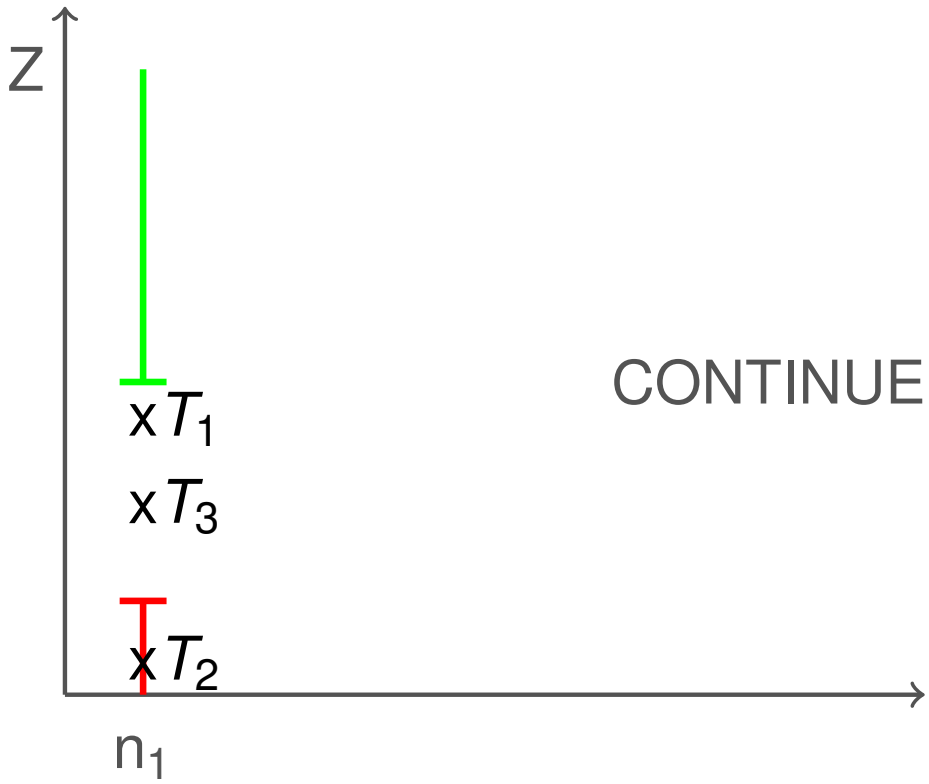
Individual null hypotheses:

$$\begin{aligned} H_1 : &\quad \mu_1 \leq \mu_0 \\ &\vdots \qquad\quad \vdots \\ H_K : &\quad \mu_K \leq \mu_0 \end{aligned}$$

Teststatistics: $Z_k = \frac{\bar{X}_k - \bar{X}_0}{\sigma\sqrt{\frac{2}{n}}}$ for $k = 1, \ldots, K$

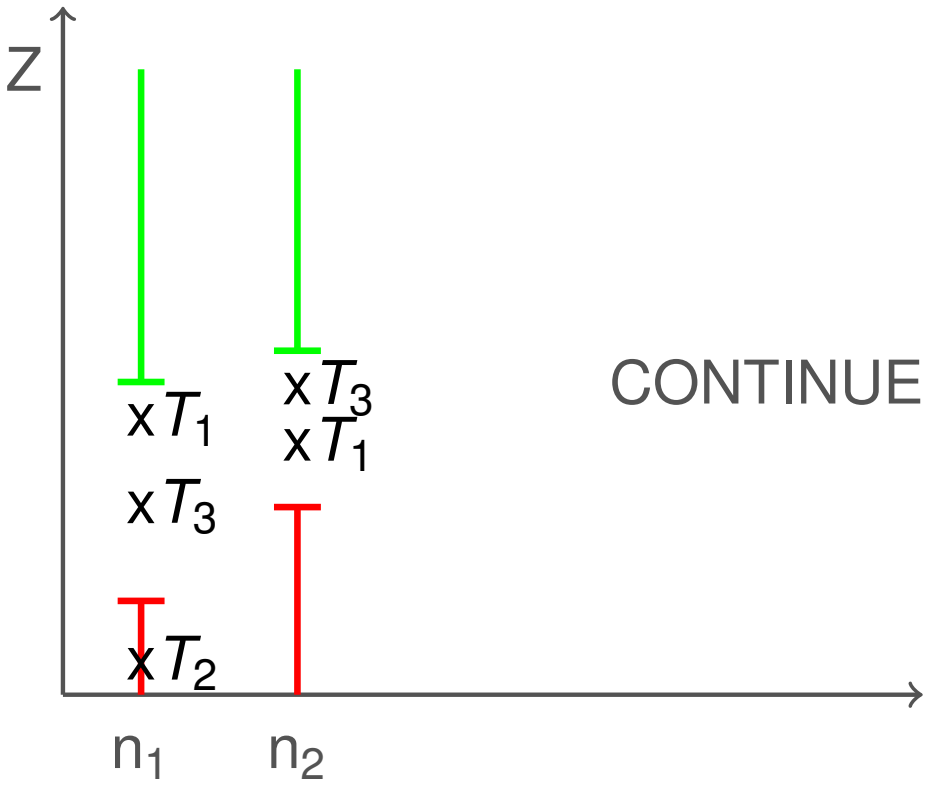
Familywise error rate (FWER): $P(\text{reject at least one true } H_k) \leq \alpha$

A multi-arm multi-stage design



(Magirr et al, 2012)

A multi-stage design



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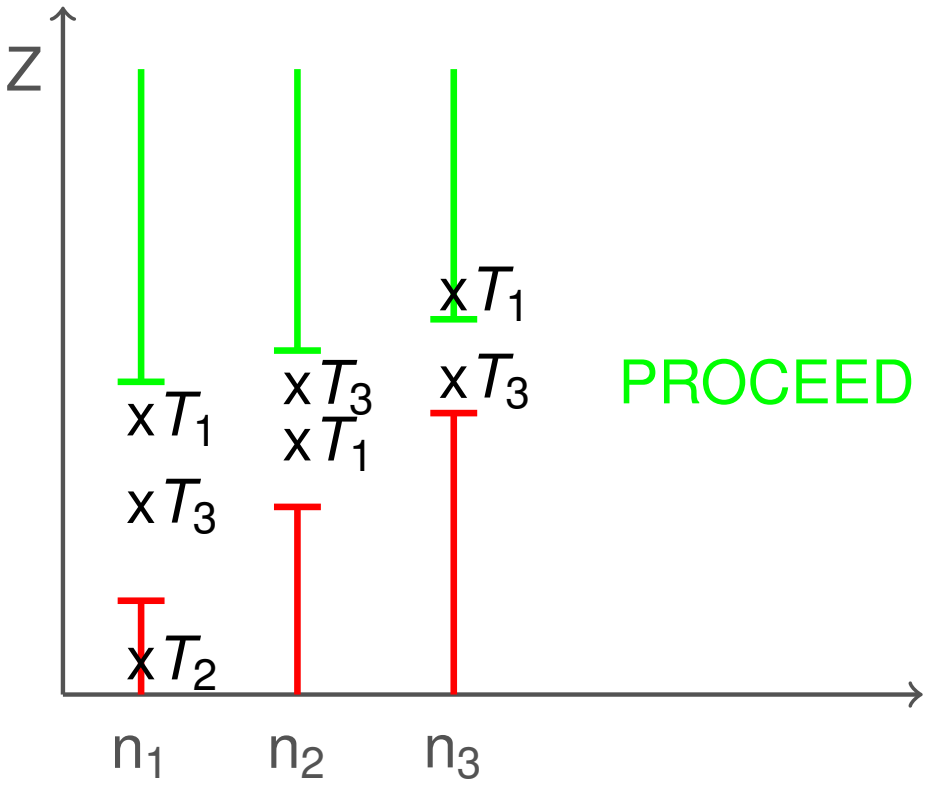

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More Multiple Testing

- J-stage trial $\Rightarrow$ up to $4J$ hypothesis tests.

Strong control of FWER

$$P(\text{reject at least one true } H_k) \leq \alpha$$

Weak control of FWER

$$P(\text{reject at least one true } H_k \mid H_G) \leq \alpha$$

Fact: for this design, Strong control of FWER $\Leftrightarrow$ Weak control of FWER (Magirr et al, 2012).

Computing $P(\text{reject at least one true } H_k | H_G)$

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Problem: Test statistics are correlated due to the common control.

Solution: Condition on $\bar{x}_{0,J}$, the vector of sample means on control.

$$\alpha = 1 - \underbrace{\int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty}}_{J \text{ times}} \left[\sum_{j=1}^{J} P\left\{ \left(\bigcap_{i=1}^{j-1} B_{1,i} \right) \cap A_{1,j} \middle| \bar{x}_0, H_G \right\} \right]^K dF(\bar{x}_0)$$

- $2J - 1$ unknowns $(l_1, \ldots, l_{J-1}, u_1, \ldots, u_J)$.

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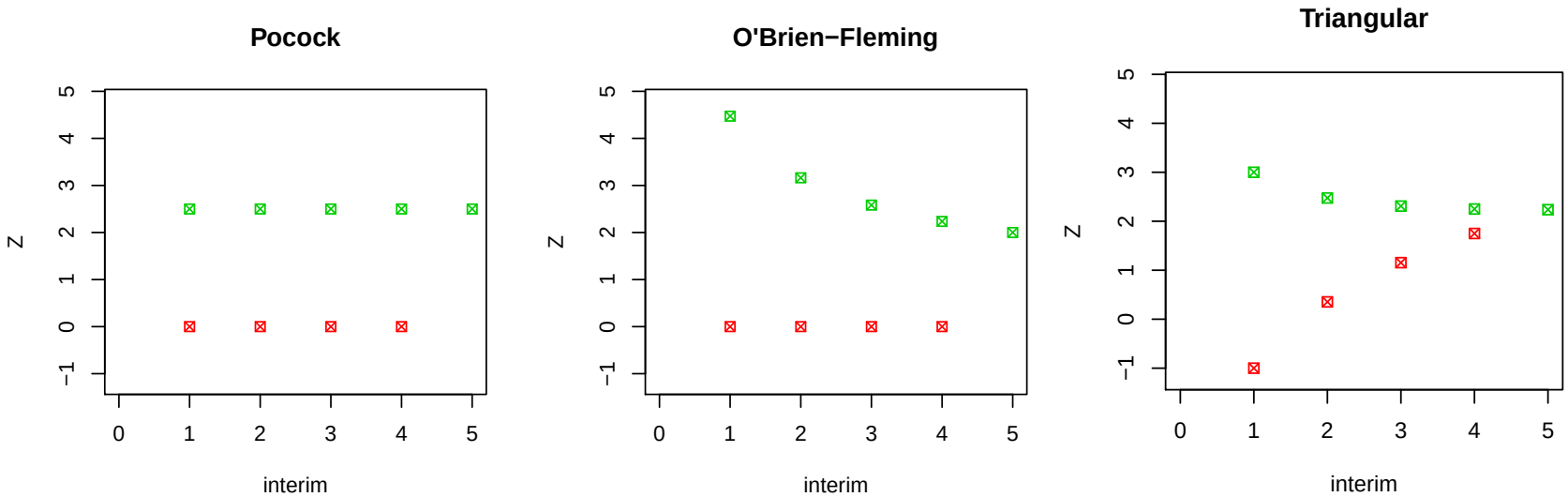
Boundary Constraints

For $J > 1$ set $l_h = g(u_J)$ and $u_h = f(u_J),\ h = 1, \ldots, J-1$.



Design considerations

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Plan submitted for funding:

- 4 active doses (20, 40, 60 and 80mg)
- 2 interim analysis with O'Brien and Fleming type boundaries
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Funded study:

- 3 active doses (20, 40 and 80mg)
- 1 interim analysis
- 370 patients to be recruited (336 evaluated needed)
- Funder was in general very happy with the design!

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Lesson: Do not be afraid to propose an adaptive design to a funding agency

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Plan:

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- Lengthy discussions
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Lesson: Make sure TMG understands decision process and buys into the stopping rules.

A surprise

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- 10% patient drop-out

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Lesson: An adaptive design does not always reduce sample size but here improved decision making.

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A buddy system

- First multi-arm multi-stage design done by this CTU
- Worked closely with CTU statistician and provided oversight
  - e.g. CTU statistician drafted stat section for application, protocol, SAP. . . I commented/refined.
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Lesson: An adaptive design does not prevent risk of over-interpretation of findings that have not been pre-specified.

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Literature

Chow SC, Chang M, Pong, A (2005) Statistical consideration of adaptive methods in clinical development. *Journal of Biopharmaceutical Statistics*, **15**(4), 575–591.

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