Implementing adaptive designs

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Idea

Modify an ongoing trial by design based on reviewing accrued data at interim to enhance flexibility without undermining the study’s integrity and validity.

(Chow et al. 2005)
The TAILoR study

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).
Multi-arm multi-stage trials

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

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

$$H_1 : \mu_1 \leq \mu_0$$

Individual null hypotheses:

$$\vdots$$

$$H_K : \mu_K \leq \mu_0$$

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

Familywise error rate (FWER): $P(\text{reject at least one true } H_k) \leq \alpha$
A multi-arm multi-stage design

\( z \)

\( xT_1 \)

\( xT_2 \)

\( xT_3 \)

\( n_1 \)

(Contiue)

(Magirr et al, 2012)
A multi-stage design

\[ xT_1 \]
\[ xT_3 \]
\[ xT_2 \]

\[ n_1 \]
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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
- Method developed for this purpose (Magirr et al., 2012)

Lesson: Do not be afraid to propose an adaptive design to a funding agency.
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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!
Design considerations

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- Decision about stopping arms/study to be made by IDMC following pre-specified rules
- TMG to accept these recommendations

Reality:

- 2 arms recommended to be stopped
- TMG wanted to see unblinded data before confirming
- Lengthy discussions
- Argued based on probability of success at study end for stopped arms is small

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Lesson: An adaptive design does not always reduce sample size but here improved decision making.
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.
  - Strongly involved in communications around interim analysis
- In the meantime CTU has submitted at least 3 more multi-arm proposals for funding with limited involvement from us.
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**Lesson:** An adaptive design does not prevent risk of over-interpretation of findings that have not been pre-specified.
Some other considerations

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• Drug supply

• Duration of study and sample size unpredictable

• Funding
