Issues in current evaluation of adaptive designs in clinical trials by Ethical Committes: some real experiences

SISMEC – February the 2nd, 2007

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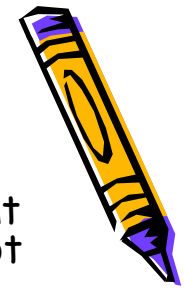
Sigma-tau



Experiences of Sigma-tau

- Only in the field of sample-size re-assessment (SSR), specifically use of blinded internal pilot studies.
- In dialysis: SSR applied to Kidney Disease Questionnaire using the method by Gould (1992) for continuos data.
- In malaria: SSR applied to the PCR-corrected cure rate using the method by Gould (1992) for binary data.
- No major problem with ECs.

Gould AL (1992). Interim analysis for monitoring clinical trials that do not materially affect the type I error rate. *Statistics in Medicine* **11**; 55-66.

Experiences of Sigma-tau (details on statistical methods)

For Dialysis (continuous end-point):
Re-estimate the SD when 1/3 of sample reaches the end-point.
N is increased only if $N' \geq N+5\%N$.
N' cannot exceed N by more than 20%.

For malaria (binary end-point):
Sample size is computed in accordance to the following formula:
$N' = N\, p\,(1-p) / [\pi\,(1-\pi)]$
Sample size is adjusted only if an increase is required.

Legenda:

- N'=new sample size
- N=original sample size
- SD=observed SD from the pooled sample
- p=observed cure rate from the pooled sample
- π=cure rate originally used for sample computation

Why consider SSR?

- Update sample size to ensure power as desired based on interim results
- When stop for futility is also part of the SSR: minimize number of patients exposed to inferior or highly toxic treatments

Available Methods

- Internal pilot studies:
  - Adjust for nuisance parameter estimates only
  - Both blinded*(*)* and unblinded nuisance parameter estimation methods are available

(*) Both experiences of Sigma-tau in this area

- Adjust sample size to retain power based on interim test statistics:
  - Either methods that assume observed treatment effect at interim or assume original treatment effect
  - All methods adjust based on unblinded treatment difference
  - An adjustment of the final critical value based on the interim test statistic is required

Internal pilot studies

- Blinded internal pilot studies:
  - Advantage:
    - No adjustment to usual tests at end of trial
    - In-house personnel can do it
  - Disadvantage:
    - The estimate of the nuisance parameter can be wrong, leading to incorrect re-adjustment
    - Weak when there is much uncertainty about treatment effect

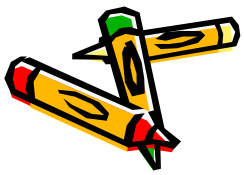
- Unblinded internal pilot studies:
  - Advantage:
    - Can provide more accurate sample-size estimate
  - Disadvantage:
    - Concern over bias resulting from knowledge of interim results
    - Requires a DMC

Recommendations

- Do not use SSR to avoid up-front decision about planning
- Before choosing SSR, evaluate use of SSR vs use of group sequential designs
- Consider that for performing SSR data acquisition and cleaning must be quick
- For choosing between blinded/unblinded SSR, evaluate the uncertainty about the treatment effect (if high, use unblinded SSR) but keep in mind that blinded methods are generally easier and better accepted by regulators
- Give adequate consideration to the confidentiality issue (do not reveal exact method for SSR; make the outcome of SSR discrete with only 2-3 options; formulate questions to the DMC with yes/no rather than numerical answers)

Recommendations (continued)

- For unblinded SSR: appoint a third party to do the calculations following a pre-specified rule and convene a DMC to review the SSR recommendation from the third party (sometime the statistician of the DMC can do the SSR)
- Plan the need to go back to EC (may be avoided by specifying in the protocol the maximum sample size)
- Carefully consider the timing to do SSR (depending mainly on the disease and the method for SSR)



Recommendations (continued)

- When applying SSR, the protocol should include:
  - The objective for SSR
  - Statistical method (only main elements for the confidentiality issue)
  - When to do the SSR
  - How to implemet it
  - How will the results be shared
  - Efficiency considerations

References

Recent review articles for internal pilot studies

- Friede and Kieser. Statistics in Medicine (2001); 20: 3861-3873
- Gould. Statistics in Medicine (2001); 20: 2625-2643
- Zucker, Wittes, Schabenberger, Brittain. Statistics in Medicine (1999); 18: 3493-350
- Jennison and Turnbull (2000), Chapter 14