

References

- Proschan, M. A., Lan, K. K., Wittes, J. T. (2006): "Statistical Monitoring of Clinical Trials: A Unified Approach" Springer *)
- Jennison C and Turnbull, B W (2000): "Group Sequential Methods: Applications to Clinical Trials" Chapman & hall *)
- Mazumdar M and Bang H (2008): "Sequential and group Sequential Designs in Clinical Trials: Guidelies for Practitioners". Chapter 16 (pages 491-512) in Rao, Miller and Rao: "Handbook of Statistics Vol 27: Epidemiology and Medical Statistics"
- Armitage P, Berry, G, Matthews, J N S (2002): "Statistical methods in medical research". 4th ed. Section 18.7 Data Monitoring (page 613-623)
- International Committee on Harmonization ICH E9 (1998): International Committee on matringuization....

 Statistical principles for Clinical Trials. www.ich.org

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- *) Available as E-book at UBIT



Why interim analyses in an RCT?

- · Early termination if treatment is superior to control
- · Early termination if treatment is more harmful than control

But:

• Interim analyses HAS implications for study design and analysis and interpretation of results



Monitoring

- Administrative monitoring: Normally makes no use of outcome data from the trial.
- Data monitoring: Concerns evidence emerging from the accumulating data on safety and efficacy of the treatment.
- Data (and Safety) Monitoring Committee D(S)MC. Regularly receives unmasked data summaries. Present recommendation for or against early termination or protocol modification.



A trial with planned consecutive inclusion of n subjects. At any interim time, a z-score test statistic can be calculated. Under H0, the z-score is N(0,1).

Group sequential trial:

Look at data k times including final look after n subjects. Possibly terminate before all n subjects are included.

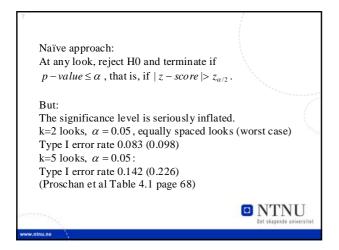
k=1: means no interim analyses k=n: means fully sequential trial

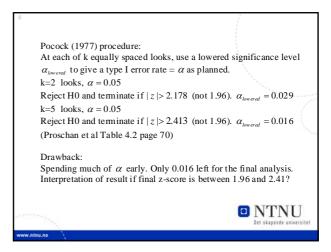


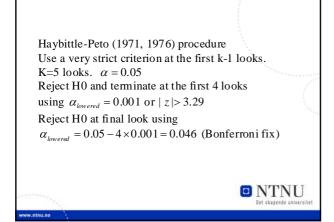
Group sequential designs for interim analyses. Alternative procedures

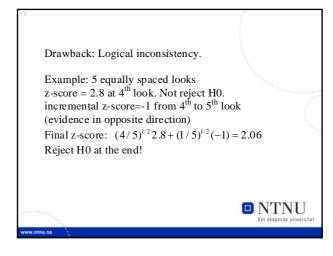
- Naïve (NOT appropriate)
- Pocock procedure
- Haybrittle-Peto
- O'Brien-Fleming
- · Alpha spending function

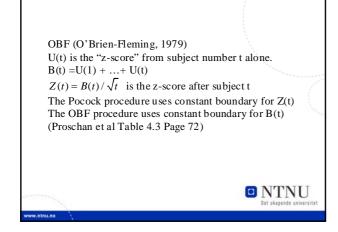


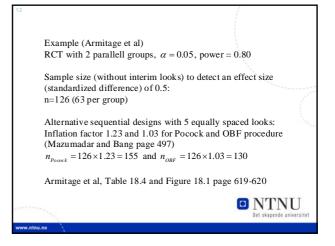












Alpha spending function

- Controls how much of alpha can be used at each look, as function of the proportion of total information observed.
- This proportion may be estimated as fraction of
 - subjects recruited
 - events observed
- Number of looks, timing of looks, need NOT to be prespecified.
- The alpha spending function must be pre-specified (for example Pocock or OBF)
- Prochan et al Table 5.1 and Figure 5.1 page 81-82.
 Figure 5.3 and Table 5.3 page 86-87

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Data-driven looks:

- Violates assumptions for the alpha spending function
- But results are approximately unaffected. Proschan et al page 89-90: "Intention to cheat" results in max 10% inflation of type I error rate.



Analysis after a sequential trial

- · Two situations:
 - After completion of trial
 - At an interim analysis
- In both situations, naïve anayses (as if data were from a fixed sample experiment) are inappropriate (see i.e. Prochan et al 2006 Chapter 7)
 - Effect size estimates and CI are biased away from 0
 - Actual CI coverage substantially lower than nominal coverage.
- P-values are too small
- "Most statisticians acknowledge that the observed effect from a trial that is stopped early overestimates the true value, but may recommend using the observed estimate for simplicity" (Proschan et al, page 114)

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Stochastic curtailment

- Early termination if it can be predicted that the final difference would almost certainly be non-significant.
- See for example Armitage et al page 622.



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Adaptive designs

- · Allows to change sample size based on accumulated data
- Two main types:
 - Using data for nuisance parameter(s) only, for example variance in a t-test.
 - Also using data for effect size



Software

(Proschan et al 2006, Mazumdar and Bang, 2008):

- · Commercial packages:
 - East (Cytel Software). *)
 - PEST (University of Reading)
 - S-plus: SeqTrial (Insightful corporation)
 - SAS: IML module
 - PASS (Number Chruncher Statistical Software, Ogden, Utah)
- Free software
 - www.medsch.wisc.edu/landemets/
 - R: Function seqmon

*) Most comprehensive (Mazumdar and Bang, 2008).

