DMC member experience: studies with adaptive designs

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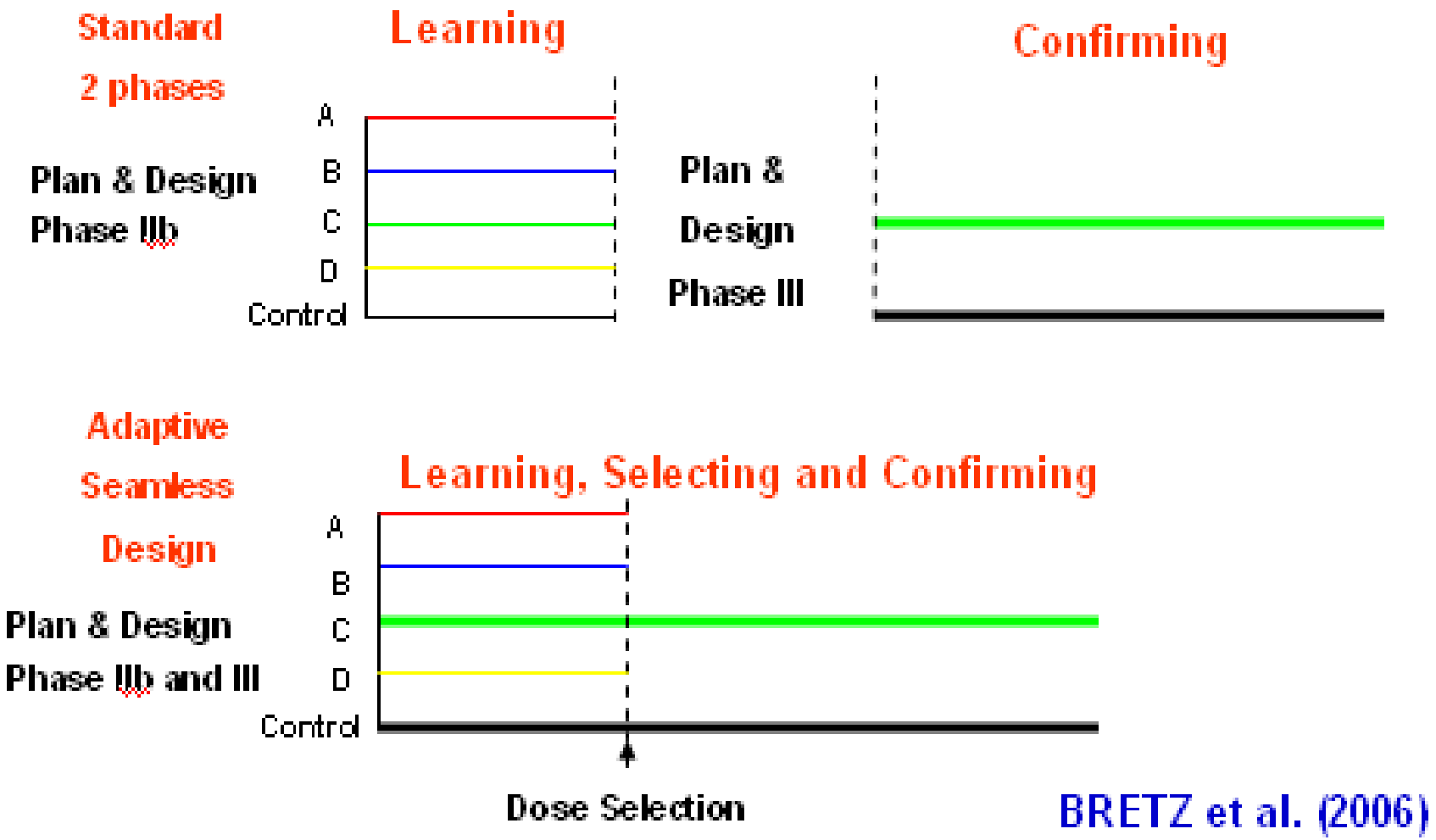
A typical application:
Dose selection and confirmative inference
(the critical issue of combining phases)

- **Scenario**
- k (multiple) doses, Placebo, parallel groups, balanced
- Many-one comparisons of doses with Placebo
- Individual inference at the multiple level α,
  e.g., by a sequential adaptive Bonferroni, Dunnett, Hochberg or strictly hierarchical test procedure

BAUER & KIESER (1999)
HOMMEL (2001)
POSCH et al. (2005)
BRETZ et al.(2006)
KÖNIG et al. (2007)

Comparison of ASD for treatment selection with separate phase II and III trials (1)



BRETZ et al. (2006)

A very early try - phase II study on Eniporide in acute myocardial infarction

(ZEYMER et al., *JACC* 2001)

- The drug is administered after hospital admission
- Primary endpoint: cumulative release of the enzyme α-HBDH within 72 hours after drug administration

- Primary objective: investigate cardioprotective effects, safety and dose finding
- Multinational, double blind, randomized, placebo-controlled, and adaptive two stage dose finding study with parallel groups

Study design

(Tiemann et al., *Heart Drug*, 2001)

- Product test, α=0.025 (one-sided), α_1=0.008 (early rejection), α_0=0.7 (stopping for futility), c_α=0.0038
- First stage:
  - placebo and 4 doses, 100 patients per group
  - proof of principle by a linear trend test
- Aim of the interim analysis
  - obtain some initial evidence of efficacy
  - select doses for stage 2
  - determine sample size for stage 2

Decisions in the interim analysis

- Maintain all trial procedures (business as usual)
- Selection of double blind doses 2 and 3 and placebo for 2nd stage (medians P: 44.2, D_1: 45.3, D_2: 40.2, D_3: 34.0, D_4: 43.4; $p_{trend} = 0.12$)
- For the proof of principle in the 2nd stage a one sided test for dose 3 versus placebo is planned
- The individual doses will be tested in a hierarchical manner
- To achieve a conditional power of 90 % 316 patients per group are needed for stage 2 (using the variance estimate in the interim analysis

Final analysis

- The t-test D_3 versus P: $p_{\geq}$=0.55
- No rejection of H_0 (no effect at all)

- **Judgement of the company biometrician (with which I sympathize):**

  - a small dose finding study followed by a large phase III study would have needed a much higher sample size,
  - two separate studies would have required a larger sample size and longer time
  - a conventional dose finding study would have required a higher sample size either

Preparation for the decisions

- External statisticians (Department of Medical Statistics, University of Vienna, **P.B., G.S., M.P.**) performed the interim analysis on an up to date data set transferred to Vienna less than a week before the meeting of the decision board
- The statistical analysis has been prepared extensively using test data
- The calculations of the main analyses have been evaluated by an independent analysis performed by the company statistician
- Important information on safety had been updated even later
- Extra monitoring capacity was required to get a “real time” data set
- A proposal for adaptations was made by the external statisticians in the interim report
- Altogether a bone-breaking task!

The decision board

External statisticians
Steering Committee Chair (P.I.)
DSMC Chair

Company Statistician
Company project leader
Company safety expert

Few other people from the company including an expert for finances

- The decision had to be performed within two days at a neutral location (University of Vienna)

The information provided to the board

- The whole data base was available on computer, so that, e.g., on demand individual safety information could be retrieved “online”

- There was a phone inquiry about the form of the dose response curve to external experts for the drug in the company not sitting in the board
- To my remembering the decision was performed without any support or advise from outside (which, because of the adaptive design strategy, I would not have considered as a major concern anyway)

Going on

- The company had prepared the drug supply for several “plausible” selection strategies
- The drug batches have been replaced in the centres without creating too much white space
- Investigators remained blinded with regard to the selection
- The decision in the board was maintained when planning the second stage.
  - **It is crucial to adhere to the design of the second stage, once chosen!**
  - (Using the concept of preserving the conditional error even further design modifications could have been made)

?

- I am convinced, that the people involved in this pioneering study tried to do and did an honest job
- The clear negative result of the study and its timely reporting in the literature are supporting that
- However, the way all these decisions have been made are in contradiction to existing guidance documents, e.g.,

“Guideline on Data Monitoring Committees”

(EMEA, January 2006**)**

“Establishing and Operation of Clinical Trial Monitoring Committees”

(FDA, March 2006**)**

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EMEA - Guideline

- "… or in case of complex study designs where a modification of the study design based on unblinded interim data is intended. In such a situation the use of an independent DMC gives more credibility to the process. However, major design modifications are considered exceptional and regulatory advice with respect to the acceptance of the planned procedure(s) should be sought in advance."
- Potential candidates for a DMC membership should have no financial interest in the outcome of the study. … any person (not only employees of the sponsor) involved in the conduct of the clinical trial (e.g. investigators) should not serve on the DMC."

FDA- Guidance

- “We therefore recommend that DMC members for a given trial not include investigators in that trial”
- “Knowledge of unblinded interim comparisons from a clinical trial is generally not necessary for those conducting or sponsoring the trial”
- “We recommend that sponsors avoid appointing to a DMC any individuals who have relationships with trial investigators and sponsor employees that could be considered reasonably likely to affect their objectivity”
- “Unblinded interim data and the results of comparative interim analyses, therefore, should generally not be accessible by anyone other than DMC members or the statistician(s) performing the analyses and presenting them to the DMC.”

FDA- Guidance (cont.)

- “Certain types of changes to the protocol, however, such as changes in the primary endpoints, could have substantial impact on the validity of the trial and/or its ability to support the desired regulatory decision if they potentially have been motivated by the interim data. We recommend that sponsors discuss proposed changes of the latter type with FDA before implementation.”

- **Do we need a revision of the guidelines?**

  (Although acknowledging the regulatory need for clear rules to ensure integrity and persuasiveness of results from clinical trials!)

Some points to consider

- Can the decisions in adaptive designs be made by a board independent of the sponsor**?**
- Should the P.I. be involved in actually treating and assessing patients?
- Do we need regulatory people in decision boards of adaptive clinical trials?

In the SAN case control study on analgesics and nephropathy regulatory authorities (D, A) nominated members of the **S**cientific **A**dvisory **C**ommittee