DMC membership experience

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EMA GUIDELINE ON DATA MONITORING COMMITTEES

"Clinical trials frequently extend over a long period of time. Thus, for ethical reasons it is desirable to ensure that for patients participating in such trials there is no unavoidable increased risk for harm. On the other hand it is also important to ensure that a trial continues for an adequate period of time and is not stopped too early to answer its scientific questions.

An independent Data Monitoring Committee (DMC) as a group of experts external to a study that reviews accumulating data from an ongoing clinical trial might serve such tasks. While in general safety monitoring should be the major task for a DMC, other aspects of a clinical trial (e.g. study integrity, design aspects) might also be assessed by a DMC. However, it should be noted that a DMC is not needed for all clinical trials."

How did all that start?

- No ethical committees
- No boards
- No infomed consent

‚The medical doctor is the expert to decide whether and how an experiment should be performed as soon there is uncertainty about which treatment should be applied against a particular disease. Patient information may only have a negative impact on the course of the trial, because of non-compliance or dropping out‘

- However, in an area where so many different interests are focusing measures are needed to come to good decisions, to care for patients‘ safety and autonomy and to avoid conflicts of interest!

A very recent experience

- Membership in an independent data monitoring board of a clinical trial in oncology
- IDMC (independent data monitoring committee)
- IC (interface committee)
- SC (steering committee)

- Only the IDMC has access to un-blinded data
- Some members of the IC are employees of the sponsor

Communication of the IDMC Recommendations

- … At each interim analysis, the IDMC will recommend that the trial either continues or stops. The IDMC may also recommend a protocol amendment.
- IDMC makes recommendations to the Steering Committee through the Interface Committee (IC).
- The IDMC Chair will notify the IC Chair of the IDMC's recommendations, … , immediately after the closed session and … within twenty four (24) hours. …

Communication (cont.)

- … If the IC decides to accept the IDMC recommendation, then the IC Chair will forward the IDMC recommendation to the Chair of the SC within the timelines …

- If the IC decides to reject the IDMC recommendation *(comment: e.g. for changes or for stopping)*, the IC Chair will prepare an IC certificate of no objection to be forwarded to the Chair of the SC … . In addition the IC Chair will prepare a communication to the IDMC Chair. …

Why?

- The sponsor may not be convinced that the IDMC members contribute sufficient expertise for taking responsible decisions?
- The sponsor may be afraid of the IDMC members to make decisions not in his interest?
- Consequently often the communicating of any efficacy data is strictly avoided and treatment codes will only be un-blinded at a special request.
- The sponsor may be afraid of an early termination of the trial due to foreseeable safety problems?
- ...

Not to forget

- How can an assessment of harm be done without balancing against the amount of benefit to be achieved in turn?
- We plan large studies to get sufficiently narrow confidence on efficacy. How difficult may decisions on (rare) safety signals become if to be taken on accumulating data without formal decision rules?
- **Don’t forget that it is the IDMC to be blamed when not reacting to emerging safety issues!**
- Also the experts in the IDMC have their share in the process and have to care for their own reputation!

Not to forget (cont.)

- It is perfectly acceptable that the company has its own interests.
- But, the team involved in the development within the sponsor is not without any conflict of interest! It may be in competition with development programs for other drugs in the pipeline.
- There may be a special pressure on the team in companies with few or no other drugs to come.
- Will the team always make sustainable decision in the overall interest of the sponsor and the public?

What to do for a member in such a case?

- After carefully studying the Charta of the different committees - and not being able to get any modification of the way how recommendations of the IDMC are going to be communicated - the chair and the statistician of the IDMC resigned. *

- E.g., we have asked for at least communicating the recommendations of the IDMC directly to the SC.

Some other actions experienced

- Stopping recruitement, centralizing the check of the inclusion criteria.
- Starting a monitoring program with additional investigations and adjudication by external experts because of an unexpected cardiac safety signal.
- Opposing sponsor‘s interpretation of the results. * *
- Poor and stable low quality of the data flow. * *
- „Proposing“ a design modification not pre-planned and suggested from outside the committee.
- Debate of poor benefit-risk balance, followed by later decisons in health systems not to refund *
- . . .

Adaptive design – some complications

- When such issues concerning committee decisions are a problem for the sponsor in a conventionally designed clinical trial, how difficult will things get if an adaptive design is run?
- It is the clue of such designs that the decision rule for the adaptive interim analysis are not laid down a priori in all their details.
- **It is perfectly understandable that the sponsor wants to have his share in crucial decisions during the development of his product!**

A historical example from the early courageous times of adaptive designs

(you may well have seen it before)

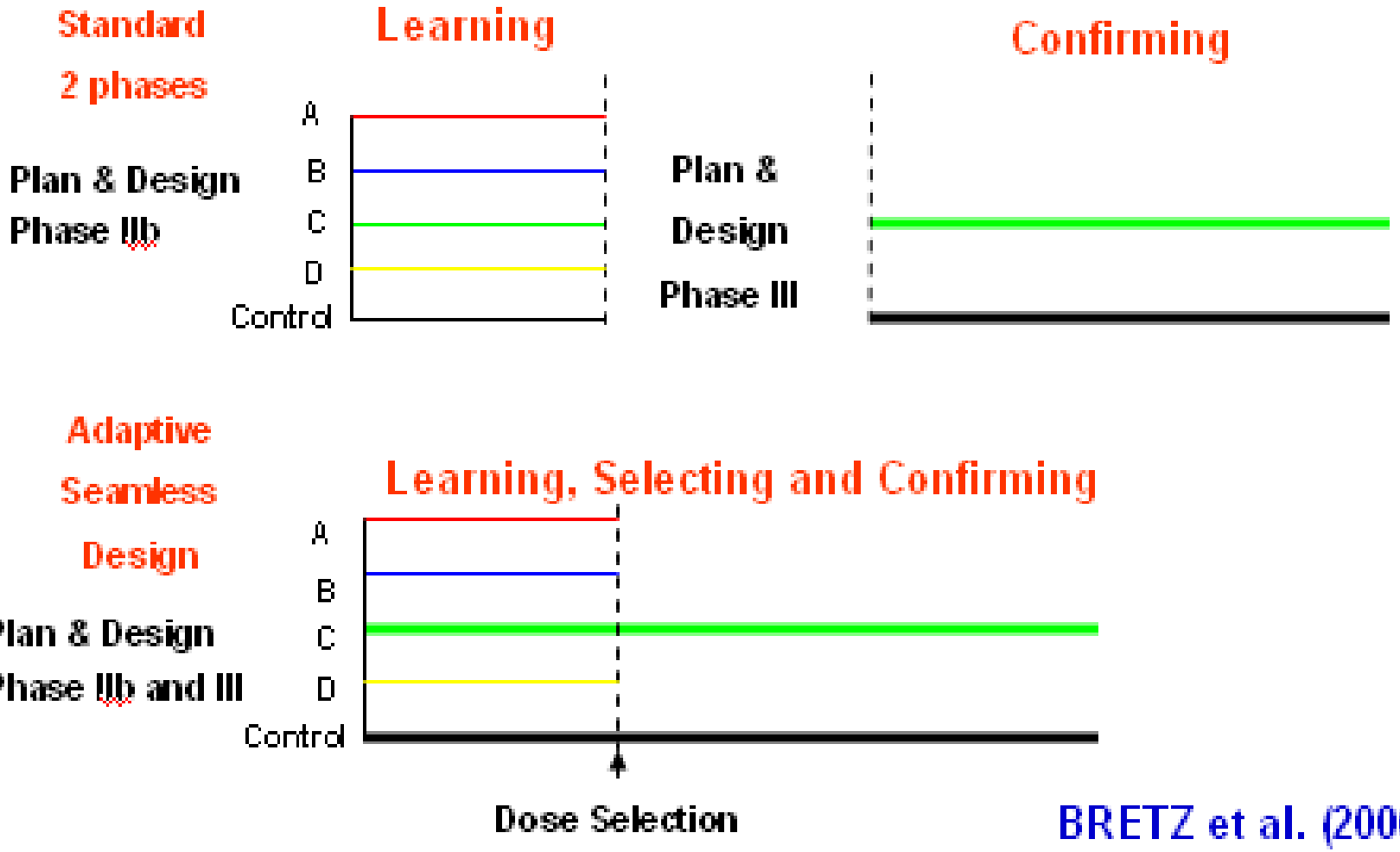
Who had and how had decisions be taken?

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 cardio-protective 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** (one may sympathize with)**:**

  - 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)

- **It was an outstanding clinical trial experience!**
- 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 publication are backing that opinion
- **However, the way all these decisions have been made are in contradiction to existing guidance documents:**

“Guideline on Data Monitoring Committees”

(EMEA, January 2006**)**

“Establishing and Operation of Clinical Trial Monitoring Committees”

(FDA, March 2006**)**

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

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.”

- **As a way out companies lay down independence of the DMC from the sponsor in the charter of the DMC. Also some (non-binding) guidance for the adaptation is given for the DMC. However it is also foreseen that the DMC may call in experts from the sponsor if deemed to be necessary.**

Some points to consider

- Which type of board should adapt the design?
- Can the decisions in adaptive designs be made by a board independent of the sponsor**?**
- Should the principal investigator as a “natural” board member be involved in actually treating and assessing study patients?
- Up to which detail can the decision when and how to do adaptations be pre-planned in advance?

- 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

Consort

Checklist of Items To Include When Reporting Harms in Randomized, Controlled Trials

(relevant items)

Outcomes

List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions). Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).

Statistical methods

Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).

Checklist (cont.)

Numbers analyzed

Provide the denominators for analyses on harms.

Outcomes and estimation
Ancillary analyses
Adverse events

Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent. Describe any subgroup analyses and exploratory analyses for harms.

A few for the road

- What are the appropriate risk sets?
- Use time till event analyses
- Should more graphical tools be used?
- Avoid obvious data errors *
- Avoid big gaps between the time limit for the analysis and the IDMC meeting
- Avoid different data bases with diverging information (depending on the reporting track) *
- The presented material may be too big and redundant (a lot of is simply skipped by the members)

A few for the road (cont.)

- Why not a IDMC for the whole development program of a new drug?
- How to integrate knowledge from prior or parallel studies into the IDMC decision?
- Define “adverse events of special interest” based on prior evidence * to improve monitoring
- Provide supportive decisions criteria (based on the available evidence) and their statistical properties

A few for the road (cont.)

- Put more emphasis on statistical methodology for safety issues
- There is still a wide field to be ploughed
- This is in the interest of the public
- - and should be also in the interest of the sponsor
- I believe that this will more and more become a quality feature in future drug development
- **Membership in a IDMC may turn out as a statistical border line experience of decisions under uncertainty**

Thank you for your patience!