The role of the Statistician in Data Monitoring Committees (DMC)

Fritz Schindel
Accovion GmbH
Marburg - Germany

Overview

- Regulatory background
- DMC membership
- Statistical contents of charter/protocol
- Resulting tasks
- Efficacy vs. safety monitoring
- Sponsor requests to DMC
- Other real life experiences…
- Interactions with regulatory agencies
- Conclusions

Regulatory background

- EMEA guideline on DMCs (Jan 2006)
- FDA guidance “Establishment & Operation of DMC” (March 2006)
- ICH E9 ”statistical principles for clinical trials” (1998)
- Some implications discussed in following slides

All studies need safety monitoring ...

- but not all need a DMC
- DMCs are
  - expensive
  - time consuming
  - cumbersome
- preferred use in controlled, large multicenter (pivotal) studies

What trials need a DMC?

- When combination of investigator, sponsor, IRB and regulatory agency insufficient to monitor safety
- When interim analysis covers efficacy related decisions (e.g. adaptive designs)
- Goal: minimize risk to trial participants, while protecting scientific validity

Examples for a DMC need

- Life-threatening diseases
- Long-term studies with non life-threatening indication
- Vulnerable population (e.g. children, pregnancy, ...)
- Interim analysis with stopping rule for overwhelming efficacy or futility
- Adaptive design with selection of a best treatment or increase of sample size

DMC membership

- Scientific expertise with indication / conduct of clinical trials
- Chair person with prior DMC experience
- Independent of sponsor, except for reasonable reimbursement of efforts within DMC
- No conflict of interest

Conflict of interest - Examples

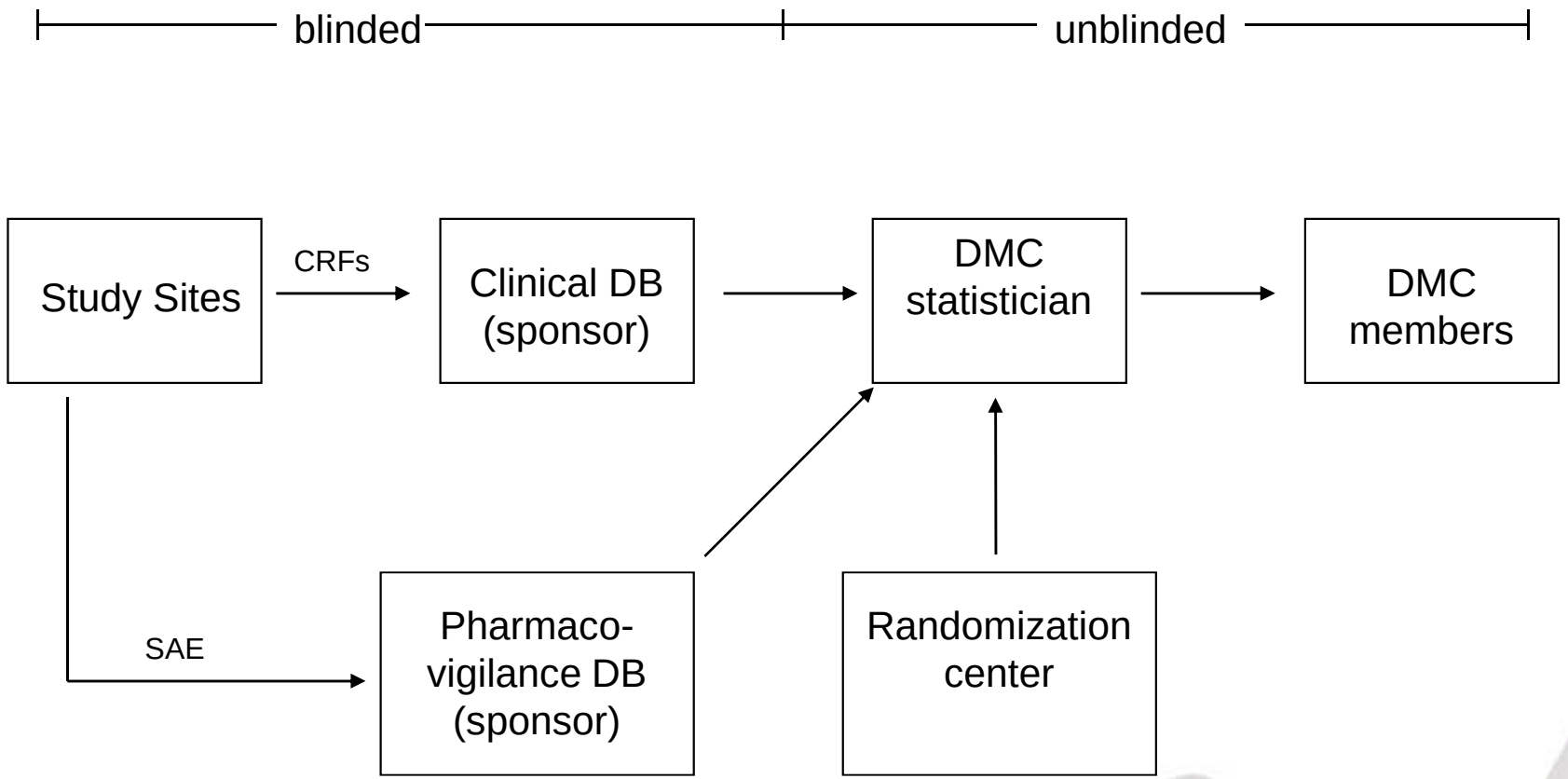
- Employees of sponsor
- Study investigators
- Planned authorship
- Financial interest in outcome (e.g., shareholder)
- Member of parallel DMC with same indication, but different sponsor

Constitutive DMC meeting

- Early enough to give feed back on study protocol
- Discuss draft charter (incl. deliverables for DMC tasks)
- Plan resource allocation, incl. those of DMC members
- Appoint chair person
- Rules for face-to-face vs. telecon meetings

Statistical contents of charter / protocol

- Essentials (e.g. frequency of interim analyses, control of type I error, futility rules) to be laid down in study protocol
- If safety only is addressed, statistical methods may be spelled out in charter document
- Charter can define role of statistician as full (voting) member vs. reporting (non voting) member
- Restrict distribution of unblinded information to DMC members



Flow of information - Example

The experienced DMC statistician ...

- is able to draft/contribute to the DMC charter, based on a study protocol and applicable guidelines
- takes over full responsibility in DMC
- reports/comments the unblinded study results to DMC members
- assures confidentiality of the analysis process/results in the respective programming environment (e.g., via internal SOP)

The experienced team statistician ...

- cannot serve on DMC since access to unblinded data is necessary
- plays a critical role in compiling data sets with adequate quality for submission to DMC statistician
- is a window person for the DMC statistician to familiarize with complex statistical protocol aspects

Safety vs. efficacy monitoring

- Repeated (unadjusted) safety monitoring is usually accepted in view of a reduced consumer (patient) risk
- No strict rules given with respect to level of significance
- Repeated (unadjusted) efficacy monitoring increases the consumer risk of facing an inefficient drug, while lowering the producer (sponsor) risk of not getting approval for an efficient drug
- This requires a strict control of the type 1 error (e.g. via an α spending approach)

Frequent intentions of interim efficacy looks

- Stop for overwhelming evidence (α spending with early, low stop boundary)
- Stop for futility (conditional power / probability of success low)
- Increase the sample size to maintain adequate power in the final analysis
- Drop a non-promising treatment arm

Futility and α spending

- Futility and α spending rules can be combined
- This leads to less conservative rules for claiming efficacy e.g. at a later stage
- Caveat: stop boundary for futility must be strictly adhered to, which is sometimes questioned by agencies

Futility and sample size adaptation

- Futility and sample size adaptation can be combined
- This limits the overall sample size increase (when effect poorer than anticipated), while stopping otherwise (lost cause in terms of budget or clinically non-relevant effect)
- Usually, this approach does not require an adjustment of the α level

The overrun case

- In the rare case of early, overwhelming efficacy, recruitment will usually progress beyond the point in time from which the stop decision was made
- This overrun requires a later, 2-nd analysis with all data acquired
- Treatment effects derived from the 2 analyses will usually lead to similar conclusions
- A noteworthy, diluted effect in the 2-nd analysis, would cast doubts on the claimed overwhelming evidence, though

Group (A, B, ..) vs. full unblinding

- Has triggered controversial discussions in the past
- Full access to actual study treatment is now recommended for DMC members (US guideline)
- Balancing of risks vs. benefits could be hampered, otherwise

Open vs. closed meetings

- Open part involves sponsor (non-voting) representatives (e.g. team statistician)
- Closed part reserved to voting members (with insight to unblinded results), & possibly consultants (e.g. from adjudication panel)
- Keep meeting minutes on both, for immediate (open part) and later (closed part) transfer to sponsor

DMC recommendations

- Continue without changes
- Consider steps to improve data quality
- Modify study protocol (e.g. stop recruitment to a subgroup, add a safety parameter)
- Termination of study

DMC is not bound to stoic (absolute) implementation of study protocol: a DMC recommendation should always consider the totality of evidence emerging from the trial, e.g. risks and benefits

To whom a DMC reports

- Trial (steering) committee with executive power
- Sponsor responsible body in charge of study conduct
- Recommendations are not formally binding…
- … but unlikely to be ignored

Sponsor requests to DMC - Examples

- Legitimate: provide pooled analyses of critical AEs, relation to prognostic variables
- Semi-legitimate: provide conditional power at time of interim analysis, e.g. for futility decision
- Not legitimate: provide p-value of treatment effect at interim analysis

Real life experiences - 1

- DMC member was also a member of the steering committee for a competing study with another sponsor
- … and therefore had to abstain from actual DMC participation

Real life experiences - 2

- DMC statistician recommended to exclude from efficacy analyses subjects with non-confirmed disease under study (lab diagnosis)
- … which later prompted FDA to disagree, since this was not supported by the protocol or SAP (clinical diagnosis)

Real life experiences - 3

- In a large cardiovascular trial, more intracranial bleeds were observed during a planned safety interim analysis with a new substance, as compared to the active reference ($0.01 < p < 0.05$)
- This triggered hard discussions on the required level of statistical significance
- Study was stopped in the end, since information from a competing trial with a similar agent went into same direction

Interaction with regulatory agencies

- Some DMC recommendations (e.g. stop for overwhelming efficacy) may trigger a controversial reaction from regulatory agencies
- Example: efficacy claim is acceptable but safety experience is deemed too small by agency
- To avoid surprises, inform agency on intended stop of trial, before execution

Conclusions (Pros & Cons) – DMCs are ...

- time consuming, expensive
- adding complexity
- can maintain study integrity
- can implement flexible designs
- can speed up a process (early stop saves costs)

… and therefore:

- weigh up pros & cons before setting one up
- and make sure it has a clear goal