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

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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 feedback 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 $\alpha$ spending

✓ Futility and $\alpha$ 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 $\alpha$ 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