Current Trends and Best Practices for Data and Safety Monitoring Board
A Joint Medical and Statistical Perspective

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Data Safety Monitoring Boards

The Medical Perspective

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Outline

- Patient Safety: responsibilities and challenges
- DSMB: responsibilities and structure
- Focus Group: DSMB experience
Past and Present

1967

- NIH advisory group recommended the establishment of DSMB/DMC
  - Safety of trial participants
  - Objective review of interim data

2010

- All NIH sponsored clinical trials are required to have a data monitoring plan
- NIH sponsored trials with clinical endpoints have a DSMB
- Many industry sponsored studies have a DSMB
- The FDA has prepared a guidance document that most likely will result in many more industry sponsored trials with a DSMB
- There is a considerable variation in operating procedures for DSMBs
What Makes Research Ethical?

- Permit withdrawal from the clinical trial
- Guarantee confidentiality
- Keep subjects informed of potential risks and benefits
- Keep subjects informed of clinical research results
- Maintain wellbeing of subjects while on trial

Emanuel, et.al. JAMA 2000
Data and Safety Monitoring Boards - Who?

- Regulatory Agencies
- Ethics Committees (IRB)
- Data Safety Monitoring Boards (DSMB)
- Sponsor
- Investigators
- Safety Monitor
Data and Safety Monitoring Boards

Why?

- Identify any safety problem promptly
- Identify logistical issues
- Evaluate trial continued feasibility
- Assess trial objectives and whether the study can be terminated early
- Ensure regular and systematic interim monitoring
- Provide an objective assessment of the interim data
- Guarantee confidentiality of interim treatment comparisons
An Independent-DSMB is Required
When?

- Long term trials that compare mortality or major morbidity outcomes
- A priori reasons for safety concerns
  - Invasive intervention
  - Serious toxicity
- Fragile populations (e.g. elderly, children)
- Population at a high risk
- Expected SAEs
- Study is large, of long duration, and multi-center
- Trials with substantial uncertainty about safety (e.g., gene therapy)

FDA Guidance 2001 (updated Dec 2005) and ICH/E9, section 4.5
DSMB - Definition

DSMB is a data monitoring committee constituted by a group of independent experts that reviews the ongoing conduct of clinical trials to ensure continuing patient safety as well as the validity and scientific merit of the trial.
Responsibilities

**IRBs**
- Oversee patients’ safety
- Initial and continuing review of protocol and related documents
- Approve informed consent
- Review reports of unanticipated problems
- Receive reports of SAEs

**DSMB**
- Oversee patients’ safety
- Review of safety and efficacy data
- Review trial conduct
- Provide monitoring plan to IRBs
- Provide summaries of study safety to IRBs at agreed-upon intervals
Challenges in Protecting Subject Safety

- Confusion about responsibilities
  - Over-emphasis on the monitoring ability of some groups (e.g., IRB)
  - Under-emphasis on DSMB and sponsors
- System is inefficient and/or there is a duplication of efforts
- Communication gaps
- Delay in disseminating summary of safety data
- Lack of consistent GCP compliance
Additional Challenges

- Lack of standards for composition and functions of DSMB
- DSMB is not always an independent body
- Not involved in data monitoring plan, if called in late
- Limited communications with IRBs
Outline

- Patient Safety: responsibilities and challenges
- **DSMB: responsibilities and structure**
- Focus Group: DSMB experience
DSMB must be developed as an independent body to objectively examine, on a regular basis, the accruing data

- Review accrued data at pre-defined time intervals
- Monitor the safety of trial
  - Assess frequency, severity, and types of AEs
  - Interim analysis
- Evaluate validity and scientific merit of trial
DSMB Responsibilities (Continued)

- Evaluate accrued data with regard to efficacy and toxicity
- Recommend termination or continuation of study
- Recommend other study modifications
- Assess study conduct
- Recommend additional analyses
Monitoring and Oversight

Logistics

- Rates of recruitment, ineligibility, non-compliance, protocol violation(s) and drop-out
- Completeness of data
- Balance on subject group randomization on important variables
- Recommendations on potential issues

Research

- Ensure adherence to approved protocol
- Monitor informed consent
- Monitor integrity of research data
Monitoring and Oversight (Continued)

Safety

- Comparison of adverse event rates in each study arm
- Safety of subjects
  - Adverse Events
- Consideration of individual events of particular concern
  - Deaths possible related to study drug
- Assure that risk-benefit ratio remains acceptable

Outcomes

- Response variables (endpoints)
- Interim variables
Membership must be broad enough to include biostatistics and clinical trials experts

DSMB must meet regularly to review safety (lack of efficacy is considered to be a safety issue)

DSMB must exercise independence and flexibility

DSMB must document processes and decisions

Membership must be free of potential conflicts of interest

Only DSMB members receive unblinded data from the data analysis center

Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (November 2001)
Generally Accepted Principles

- Certain types of trials should have formal DSMB
- DSMB should be multidisciplinary
- A charter should describe the operations and procedures of the committee
- DSMB members should be free of conflicts of interests
  - Any basis for preferring the outcome to be in one or the other direction
  - Any ability to influence the trial conduct in a role other than that of DSMB member
- Interim data should be considered highly confidential
DSMB Composition - Multidisciplinary

- Medical experts on the disease and target organ toxicity therapeutic areas
- Medical expert on drug safety/risk management
- Biostatistician with expertise in clinical trials
- Other members depending on the nature of the study (e.g., ethicist, pharmacologist, patient advocate)
Outline of Charter

- Meeting format and frequency
- Reporting responsibilities
- Stopping guidelines
- Minutes
- Procedure to ensure confidentiality
- Conflict of interest

Ellenberg, et al., Data Monitoring Committees in Clinical Trials, 2002
**DSMB Meeting Format**

- **Open Session**
  - Sponsor: Protocol Chair, Executive Committee
  - DSMB medical members, blinded and unblinded statisticians
  - Progress report

- **Closed Session**
  - DSMB medical members and unblinded statisticians
  - Blinded data by treatment group

- **Executive Session**
  - Session may be called only if necessary
  - Only includes voting members of DSMB

- **Debriefing Session**
  - DSMB medical and statistical members and sponsor
DSMB Reports

- Completeness of data for endpoints by treatment group
- Adherence to assigned treatments
- Baseline comparability by treatment group
- Assessment of planned versus actual trial duration
Sources of Data

- CRFs, SAE data, randomization codes
- Up-to-date enrollment information
- Protocol violations/exemptions
- Special assays/lab tests that could un-blind sponsor
- Last-minute endpoint or mortality data
- Data quality and timeliness is vital
DSMB Confidentiality

- Interim data reviewed by the DSMB must remain confidential.
- Members must not share interim data with anyone outside DSMB.
-Leaks can affect:
  - Patient recruitment
  - Protocol compliance
  - Outcome assessment
  - Trial integrity and support
Recommendations

- Aside from the statistician who prepares the report, no one else is present during review of treatment comparison.
- It is not recommended for the sponsor to attend the close session of the DSMB meeting or to receive the interim summaries.
- The inclusion of other participants to the close session of the DSMB meeting requires justification.
Decision Making Process is Complex

- Internal consistency
- External consistency
- Benefit/risk balance
- Current vs. future patients
- Clinical and public health impact
- Statistical issues
Considerations to be Made

- Inclusion of irrelevant material interferes with DSMB job
- Highlight most relevant results
- Disposition of reports
- File copy of closed reports
- Written summaries of closed data
- Distribution of open reports
- Meeting summary to IRBs/ECs
Monitoring Recommendations

- Continue protocol un-modified
- Modify protocol
- Terminate trial
Sponsor Access to Interim Data for Planning Purposes

- Desire is understandable . . . but may render trial results uninterpretable by the agency.
- Potential for unanticipated extreme finding of effectiveness, which might create an ethical imperative to stop the trial.
- Sponsor should see minimal information.
- Formulate written questions, in ‘yes/no’ format.
- Sponsor should receive information only on questions posed.
- SOP to identify “need to know” individuals.
Summary

- A DSMB can be most effective in its role of protecting the interest of patients, if it is independent of the sponsor and trial investigators.
- Operating procedures should be agreed upon in advance.
- An informed statistician who performs interim analysis is important.
- To carry out interim analyses data must be collected in a timely manner.
- Reports should focus on comparisons of clinical outcomes and their validity.
Outline

- Patient Safety: responsibilities and challenges
- DSMB: responsibilities and structure
- **Focus Group: DSMB experience**
Focus Group - The Experts' Opinion

- Multiple therapeutic areas
- Current practice
- Independence of DSMB
- DSMB composition
- Preparing the charter
- Importance of the DSMB kick-off meeting
- What to review during the open session
- Pitfalls during the close session
Focus Group - Therapeutic Areas

Number of MDS

- Cardiovascular: 2
- CNS: 1
- Diabetes: 1
- Genetic Disease: 2
- GI: 2
- Hematology: 2
- Inflammation: 2
- ID: 1
- Oncology: 1
- Pediatrics: 2
- Respiratory Disease: 2
Focus Group -
Years of Experience on DSMB

Years of experience

Cardiovascular: 7
CNS: 3
Diabetes: 5
Genetic Disease: 10
GI: 9
Hematology/Inflammation: 9
ID: 8
Oncology: 10
Pediatrics: 4
Respiratory: 10

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Are DSMB members more often recruited by an independent DSMB service or by the sponsor?
Have there been situations where additional voting members were needed with broader expertise?

- Specialists for safety signals: 62%
- Ad-Hoc members: 12%
- Ethic specialist: 13%
- Replace absentees: 13%
Are all the information needed always included in DSMB charters?

No adjustment needed

83%

17%

More details and clarity
Do you find it useful to have a kick-off meeting? What should be covered?

- Study end-points (19%)
- Previously Reported AEs (IB) (19%)
- Action items (19%)
- DSMB procedure (16%)
- Tasks & responsibility (16%)
- Ethical issues (11%)
What is needed to be shared during the open session to engage in a successful and efficient close session discussion?

- Review Charter: 26%
- Review TGL: 18%
- Review Protocol: 10%
- Experienced chairman: 26%
- Tasks and responsibilities: 20%

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What are the most common pitfalls in closed sessions?

- Unclear and incomplete presentation: 25%
- Conflict of interest: 18%
- Never experienced issues: 14%
- Challenging safety profile: 25%
- Unclean data: 18%
**Conclusions**

**DSMB Characteristics**

*Should be: Independent*
- Avoid conflict of interest
- Protect patient safety
- Assure trial integrity

*Should be: Multidisciplinary*
- Broad medical expertise in the voting panel
  - Disease specialists
  - Therapeutic area experts according to study treatment safety profile
- Medical drug-safety and risk-management expert
Thank you for your attention

Any Questions?
Data Safety Monitoring Boards

The Statistical Perspective

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Outline

- Statisticians Roles’ in the DSMBs
  - DSMB Statistician
  - Independent Statistician
- Data Analysis Centers
- Best Practices for Data Analysis Centers
- Interim Safety Analyses
- Interim Efficacy Analyses
- Statistical Stopping Rules
  - Overwhelming Efficacy and Futility
- Ethical Considerations of Study Stoppage
- Summary and Conclusions
Statisticians and DSMBs

Statistical member of DSMB

- Usually a voting member of DSMB
- Experienced in the trial indication
- Well versed in statistical methods for safety analysis
- Expertise in analysis methods for adaptive designs
Statisticians and DSMBs (Continued)

Independent Statistician

- The lead statistician from the Data Analysis Center in charge of producing the unblinded analyses for the DSMB
- Usually a non-voting member of DSMB
- Well versed in statistical methods for safety analysis
- Expertise in analysis methods for adaptive designs
The Data Analysis Center (DAC)

- An independent team of statisticians /programmers
- May be a part of an independent DSMB service
- Prepares Tables, Listings, and Figures (TLF) for the DSMB
- The DAC must remain independent from the statistical team analyzing the data for the CSR
- “Firewall” between the team providing DAC services and the team working on CSR analyses
Data Analysis Centers (Continued)

The independent statistician is the liaison between the DAC and the DSMB:

- Attends DSMB meetings (non-voting member)
- Ensures TLF are produced per DSMB specifications
- Provides summaries of analyses to the DSMB in advance of meetings, as needed
- Presents the results to the DSMB during the meetings, as needed
DAC Best Practices

- Unblinded interim results must be accessible only to the DSMB and the DAC
- SOPs must be in place to ensure compliance in all aspects of statistics and programming
- SOPs for interim analyses include:
  - Processes to prevent accidental unblinding
  - Communication paths and flow of data
  - Guidelines for stopping a trial
DAC Best Practices (Continued)

- The DAC and/or the sponsor will prepare table shells and, if needed, a brief SAP for the consideration of the DSMB
- The DSMB will provide comment and input to ensure the analyses address all pertinent issues
- Throughout the trial, the DSMB may add and modify analyses in consultation with the DAC statistician
DAC team members must be trained on the study specific documents including but not limited to the DSMB charter.

The DSMB charter usually specifies the rules around blinding/pseudo-blinding of the TLF and guidance regarding data flow.
The DAC usually prepares two versions of the TLF

- For sponsor use: Blinded TLF using mock randomization codes or showing all data in only one column – no by-treatment group analyses
- For DSMB use only: Unblinded TLF
- Some DSMB charters call for pseudo-blinding even for the DSMB version of the TLF
Interim Safety Analyses

- The number one objective of any DSMB is monitoring the safety of the trial
- In most clinical trials, safety is not analyzed using significance testing - neither for the interim nor for the final analysis
- For DSMBs, the safety results may be placed in the proper context of random variation using confidence intervals
The main decision made by DSMBs at the end of each data review meeting is whether to stop the trial for reasons of safety.

Statistical rules for stopping for safety are usually not pre-specified in the charter.

Some charters pre-specify rules of thumb based on clinical considerations.
A special case: Trials in life threatening diseases with survival as primary outcome:

- Greater emphasis is placed on statistical testing as a consideration for stopping the trial
- One challenge for DSMBs is to separate death due to disease versus death due to treatment
- DSMB may stop the trial for high mortality rates based on medical and statistical considerations
In some indications/patient populations trials may be stopped by DSMBs due to a high incidence of a specific AE or SAE

- Example: AEs indicative of Drug Induced Liver Injury (DILI)
- A Fisher’s exact test or preferably the corresponding exact confidence interval, may be used to compare the incidence in experimental versus control arms of the trial
Interim Safety Analyses (Continued)

- Although pre-specified statistically-based stopping rules for safety are rarely used, some statisticians advocate such rules because they are objective and consistent, and some physicians prefer to have such rules available.

- If a statistically-based rule is proposed for stopping a trial for safety, it should be allowed to be overridden based on clinical considerations.
Interim Safety Analyses (Continued)

- No adjustment to p-value of the final efficacy analysis is required for having a safety stopping rule in a clinical trial.
- All deliberations and rationale explored by the DSMB leading up to a study stoppage due to safety concerns must be recorded and archived.
Interim Efficacy Analyses

- DSMBs are increasingly taking on responsibilities with respect to interim efficacy analyses and implementing stopping rules based on efficacy.
- The DSMB can stop a trial based on:
  - Overwhelming efficacy
  - Futility
- The DSMB may also take on the responsibility of interim analysis for sample size re-estimation.
Interim Efficacy Analyses (Continued)

- Statistical inference at an interim time-point is conducted to make an early decision on efficacy based on the primary outcome.
- Trials may incorporate a stopping rule based on a Type I error boundary (e.g., O’Brien – Fleming).
- Trials may incorporate a futility criterion (e.g., based on conditional power).
- Some trials incorporate both boundaries/rules.
Interim Efficacy Analyses (Continued)

- Draft FDA guidance issued in February 2010: Adaptive Design Clinical Trials for Drugs and Biologics
- Covers all aspects of adaptive trials including designs that allow trial stoppage for overwhelming efficacy or futility
- Discusses the role of DSMBs in enabling the conduct of unblinded interim efficacy analyses without jeopardizing the study blinding and invalidating the trial results
- Provides guidance on the statistical aspects that should be pre-specified in the protocol and the SAP
- Provides a detailed discussion of the concerns associated with interim efficacy analyses and guidance on avoiding pitfalls
Interim Efficacy Analyses (Continued)

- Why stop for overwhelming efficacy?
  - To avoid additional cost
  - To avoid exposing more patients to a less efficacious control treatment – especially if the trial is placebo controlled
  - To bring the efficacious treatment to market earlier – helping the patients and benefiting the sponsor

- Sometimes stopping is not an option: additional data needed for approval – may adapt trial to switch placebo patients to active drug

- P-value for the primary analysis at the final time point must be adjusted
Interim Efficacy Analyses (Continued)

- Why stop for futility?
  - To avoid additional cost
  - To avoid exposing more patients to a less efficacious experimental treatment

- Interim analysis/adaptive techniques for analyses of futility are mostly based on conditional power - no impact on Type I error

- No adjustment to p-value of the final analysis for the primary endpoint
Stopping Trials for Overwhelming Efficacy

Group Sequential Methods

Example: O’Brien - Fleming

- Start with relatively small alpha for first interim look and increase with every subsequent look
- Fixed and pre-planned number of interim looks – not flexible

Simplest example:

- One planned interim analysis mid-study
- Test efficacy at $\alpha=0.006$ for the interim analysis
- Test efficacy at $\alpha=0.044$ for the final analysis
Alpha Spending Methods

Example: Lan DeMets

- Flexible version of Group Sequential Design
- Not required to pre-specify
  - Number of interim looks
  - Timing of interim looks
**Stopping Trials for Futility**

**Stochastic Curtailment:** Stop study at interim time-point if it is “highly probable” that the null hypothesis will not be rejected at the final analysis given:

- The assumed treatment effect
- The actual observed data so far
Stopping Trials for Futility (Continued)

- Most commonly used tool is Conditional Power
  - Stop trial if CP is below threshold
- If a trial result is “negative” at the interim look, the Conditional Power can be calculated to evaluate the probability that the current trend improves sufficiently, so that the final analysis renders a “positive” result (e.g., evidence of treatment effect)
Other Approaches:

- Futility Stopping Boundaries — “β spending”
  - Using specialized software (such as EaSt, PEST)
- Predictive Power
- Bayesian Methods: Predictive probability
Examples from literature of trials with statistically driven safety stopping rules that may have been stopped too late

Hedenmalm, 2008 – *European Journal of Clinical Pharmacology*

- References 4 recent examples of delayed study stoppage by DSMBs as a result of pre-determined safety rules
- One study of a lipid lowering drug was not stopped at an interim time-point even in the presence of a clear safety signal because the p-value comparing mortality against control group was 0.052
Stopping Rules: Ethical Concerns (Continued)

A different set of ethical concerns arises for studies that are stopped early for efficacy especially in oncology:

- Cannistra, 2004 - *Journal of Clinical Oncology*

- Study is stopped early for overwhelming efficacy based on pre-defined analysis of the primary efficacy variable (e.g., PFS)

- Due to study stoppage, not enough data to conduct meaningful analyses on important secondary efficacy variables that require more time to evaluate properly (e.g., OS and QOL)
Summary and Conclusions

- Statisticians play a vitally important role in DSMBs and are an integral element in ensuring:
  - the safety of the trial subjects; and
  - the integrity of the trial

- Statistics are used in a variety of ways for interim monitoring of safety and efficacy based on trial goals
Summary (Continued)

- Pre-specified statistical decision rules for study stoppage are vital tools to guide the DSMB.

- However, stopping a trial for efficacy or safety is a complex decision which requires full consideration of all relevant statistical and clinical issues.
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