Clinical Research:
Challenges and controversies in clinical trials
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Seattle
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DSMB: They told me I need a DSMB - What do I do now?

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"They told me I need a DSMB"

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Treatment effects monitoring

An ongoing process of reviewing accumulated outcome data during the trial to assess treatment effects for the purpose of determining whether to allow the trial to continue unaltered.

\TEMHist\TEMDefn

Names

- **Data and safety monitoring committee (DSMC); most common**
- **Data and safety monitoring board (DSMB); not recommended**
- **Data monitoring committee (DMC)**
- **Independent data monitoring committee (IDMC)**
- **Safety monitoring committee (SMC)**
- **Treatment effects monitoring committee (preferred, but not in common usage)**
- **Ethical committee (uncommon in US; not recommended)**
- **Policy Board (not recommended)**
- **Policy and data monitoring board (not recommended)**

\TEMHist\Names

"They told me I need a DSMB"

No one should have to tell you that you need a DSMB. You should be able to figure that out on your own. If someone has to tell you need to monitor there is something wrong with you!

\DSMB.UWa\Question

The monitoring imperative

- **Being able to research on human beings is a privilege granted by society**
- **Clinical research is a luxury of an affluent Nation**
- **Public trust in the clinical research enterprise is eroded by errant acts**
- **Useless research, no matter how harmless, is unethical**
- **Harm, in the context of trials, has two forms**

\DSMB.UWa\Duty

Trials requiring monitoring

Any trial in which the treatments have the potential for producing an adverse or beneficial treatment effect and where it is possible to detect and act upon such effects during the course of the trial.

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NIH 1979 Clinical Trials Committee

- **Every clinical trial should have provision for data and safety monitoring**
- **Provision should be approved by IRB**
- **A multicenter trial should have an independent treatment effects monitoring committee**
- **Monitoring committee should include clinicians with expertise in disease under study, biostatisticians, and scientists from other pertinent disciplines. Physicians in the study engaged in patient care should be excluded from membership**

\TEMHist\NIH1979

NIH policy for data and safety monitoring (1998)

It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-sponsored clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants.

\TEMHist\NIH1998

NIH guidance on reporting to IRBs (1999)

"Effective July 1, all multi-site trials with data safety monitoring boards are expected to forward summary reports of adverse events to each IRB involved in the study"

"The DSMB's summary report should provide feedback at regular and defined intervals to the IRBs. The Institutes and Centers should assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. For example, after each meeting of the DSMB, the executive secretary should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given day. It should summarize the Board's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform investigators of the study [of] the Board's conclusion with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to the local IRB."

\TEMHist\NIH1999

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NIH websites re treatment effects monitoring (as of 13 May 2003)

NCI

All clinical trials supported or performed by NCI require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the principal investigator/project manager or NCI program staff to a data and safety monitoring board (DSMB).

NHLBI

When should a DSMB be established? For clinical trials (intervention studies), Data and Safety Monitoring Boards (DSMBs) are established; for observational studies and registries, Observational Study Monitoring Boards (OSMBs) are established. All intervention studies must have ongoing data monitoring. Not all, however, require formal DSMB. If an institution does not appoint a DSMB for intervention study, the data monitoring may be performed, for example, by the investigator, another individual, or by the IRB.

NEI

... The data and safety monitoring plan may range from the appointment of a Safety Officer to the organization of a formal Data and Safety Monitoring Board (DSMB). Ongoing review of the data by an independent individual or DSMB assures the investigator(s) that the trial can continue without jeopardizing patient safety.

\TEMHist\NIHNow

Essential requirements for adequate monitoring

- **Timeliness**
- **Completeness**
- **Indelible linkage to study investigators**

\DSMB.UWa\Require

Implications of essential requirements

- **Real-time or near real-time visit driven data collection and entry**
- **100% data entry**
- **Continuous data flow to CC**
- **Timely harvest at CC for analysis**
- **Monitoring body commissioned to report directly or simultaneously to study investigators**

\DSMB.UWa\Imply

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Guiding principles

- Investigators set monitoring policy and rules
- Monitoring body must be linked to study investigators
- Competency in monitoring must take priority over desire for objectivity

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Objectivity vs competency

Objectivity constructs

- Masking
- Firewalls
- Stopping rules
- Look restrictions
- Isolation

Competency constructs

- Absence of restriction on # or type of looks
- Absence of CC firewalls
- Unmasked monitoring
- Unfettered discussion and review
- Investigator participation

\DSMB.UWa\ObjvsCom

Monitoring policy

- Should be specified in writing by study investigators
- Should be approved by study investigators (rare; especially in NIH-sponsored trials)
- Should be part of vetting process for members
- Should be distributed to IRBs
- Should be reflected in consent form
- Changes proposed by DSMB should be subject to ratification by study steering committee

\DSMB.UWa\Rules

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Policy and organizations questions

- **Appointing authority?**
- **Vetting authority?**
- **Conflict of interest screening?**
- **Term of membership?**
- **Attendance clause?**
- **Rules?**
- **Size?**
- **Study representation?**
- **Duties?**
- **Chair?**
- **Independence?**
- **Recommending vs decisional authority?**
- **Mode and route of reporting?**

\DSMB.UWa\OrgQues

Appointment and vetting

Appointing authority: Sponsor with advise and consent of investigators or visa versa

Vetting authority: Sponsor and investigators after disclosure of financial, scientific, and philosophical conflicts of interest

Term: Typically without term (recommended)

Attendance clause: Optional (recommended in long-term trials)

\DSMB.UWa\Appoint

Conflicts of interest (CoI)

- **Philosophical**
- **Scientific**
- **Financial**

\DSMB.UWa\CofI

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CoI screening and disclosure

- Members screened for CoI per sponsor and investigator requirements
- Vetting process includes review of CoI disclosures by sponsor and investigators
- Sponsor and investigators responsible for deciding when CoI is sufficient to disqualify
- Periodic review of CoI during tenure of PDMB

\DSMB.UWa\CoIScr

CoI reality

- All persons have conflicts of interest therefore is more realistic to strive for a "balance" of CoIs than absence of CoIs
- The more restrictive the vetting process re CoI, the greater the probably of ending up with an "Alfred E Newman Committee"
- Not all conflicts of interest are created equal
- Philosophical and scientific CoI are at least as serious as financial CoI in the monitoring process

\DSMB.UWa\CoIView

Composition principles

- Mix of "outsiders" and "insiders" (the latter in the form of study officers)
- Voting members independent of sponsor and study (ie, independent of study but not isolated from study)
- Essential expertise
- Redundancy
- Parity of membership in voting vs nonvoting members in all regards except voting

\DSMB.UWa\MemPrin

Composition questions

- Lay representative?
- Activist?
- Ethicist?
- Person with disease of interest?
- Study treater?

\DSMB.UWa\MemQues

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Membership

Size: Typically 5-7 voting members and officers of study as nonvoting members; at least 3 voting members

Disciplines/specialities: Medical/surgical, clinical trials, biostatistics, data processing and analysis

Study representation: Officers of the study at parity with voting members save for voting

\DSMB.UWa\Members

Primary duty and responsibility

Duty: To monitor accumulating results to determine whether it is appropriate to allow the trial to continue unaltered

Responsibility: To recommend results-based actions directly to study investigators or to investigators via sponsors

Comment: Increasingly, DSMBs are viewed as having decisional authority over the trial re continuation; such views to be challenged because they are at odds with ethical codes underlying research on human beings

\DSMB.UWa\Duties

Other duties?

- **Review of protocol**
- **Review of major protocol amendments**
- **Review of major study publications**
- **Review of ancillary study proposals**
- **Funding advice as requested by sponsor**
- **Performance**

Comment: The greater the array of other duties the less attention to the primary duty of treatment effects monitoring

\DSMB.UWa\OtherJob

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Operational questions

- Mode of meeting?
- Frequency of meetings?
- Stopping rule?
- Look restriction?
- Executive session?
- Masked reports?
- Pay?
- Face-to-face vs conference phone meetings?
- CC firewall?
- Access to monitoring reports?
- Reporting to IRBs?

\DSMB.UWa\OpQues

Voting and attendance issues

- Quorum (Recommendation: 2/3rds voting and nonvoting members; chair or vice chair, director or deputy director of CC)
- Proxy votes (Recommendation: No)
- Absentee votes (Recommendation: No)
- Provision of conference phone for people not able to attend face-to-face (Recommendation: No)
- Cell phone use with meeting held via conference telephone (Recommendation: No)

\DSMB.UWa\Voting

Masked monitoring?

Pros

- Increases the appearance of objectivity
- Preferred by sponsors
- Superficial appeal

Cons

- Reduces individual and collective monitoring competency
- Predicated on false assumption (ie, that the action indicated is independent of the sign of the trt difference)
- Increases the probability of undetected error
- Complicates production of reports

\DSMB.UWa\Mask

Masking options

None (trt groups identified by name)

Revealed
- Coding revealed to members at outset of reviews
- Coding supplied in envelope contained in reports to be opened at will of individual members

Imposed (Revealed only by group decision; typically requires censoring of counts to avoid telltale unmasking and presentation of safety data unmasked)
- Constant across reports and tables in reports
- Constant within report, but varied across reports
- Varied from table to table within report; constant across reports
- Varied from table to table within report; varied across reports

\DSMB.UWa\MaskType

On reasons to be wary of stopping rule?

- Impossible to specify conditions at outset that may lead to premature termination
- Rules tend to be unrealistic and mechanistic
- Does not encourage meaningful data analysis
- Over emphasizes significance testing as an analysis approach

\DSMB.UWa\StopRule

Cornfield on the preservation of p-value

If maintenance of the significance level interferes with the release of interim results (of clinical trials), all I can say is so much the worse for the significance level.

\DSMB.UWa\pValue

On reasons to be wary of CC firewalls

- Artificial and unnecessarily constraining
- Reduces internal checks and balances
- Increases the probability of undetected error
- Isolating

\DSMB.UWa\Firewall

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Look restrictions?

Pros

- **Appealing to frequentists**
- **"Preserves" p**
- **Reduces likelihood of "dredging"**

Cons

- **Reduces individual and collective competency**
- **Unlikely to be adhered to in the face of "trends"**
- **Anti-intellectual**

\DSMB.UWa\Look

Meeting issues

Frequency

Recommendation: Twice yearly

Mode

Recommendation: At least one face-to-face meeting per year; not piggy back on other meetings

Time

Recommendation: Prime time (daytime Mon - Fri)

Place

Recommendation: Convenient location to minimize overnight stays

\DSMB.UWa\Meet

Pay for voting members?

Recommendation: Yes

Amount: Modest/per meeting

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The monitoring report

- **Bound in 3 ring binder or with O rings**
- **Distributed by CC at least 5 working days in advance of meeting**
- **Sequential page numbering**
- **Front matter, including table of contents and associated page numbers and study sketch**
- **Appendix materials including consent forms and study CV**

\DSMB.UWa\Report

Reports to IRBs

When

After each mtg (face-to-face or conference phone) of PDMB data review; within 60 days of such review

Distribution

To all IRBs of record by the CC or CO

Content

Summary of materials reviewed; summary of adverse experience and recommendation (without indication as to whether unanimous)

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