Watching From Above: The Role of the DSMB

C. Michael Gibson, M.S., M.D.

Harvard Medical School

Chairman, PERFUSE Study Group

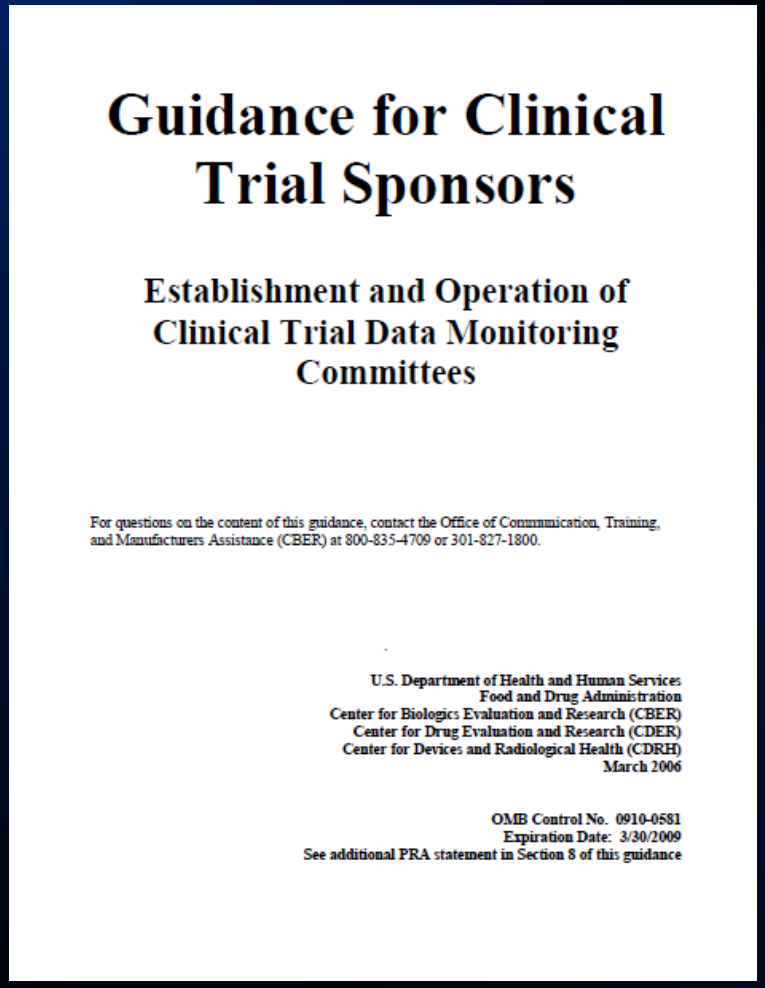
Founder and Chairman, WikiDoc & WikiPatient, The World's Open Source Textbook of Medicine Viewed 896 Million Times A Year

History of DSMB's*

- 1960- Initiated in NIH and VA trials
- 1967- NIH introduced concept (Greenberg Report)
- 1992- Operational issues defined (NIH workshop)
- 2000- DMC oversight adopted by industry
- 2005- DAMOCLES study group proposed DMC charter
- 2006- FDA guidance for Clinical Trial Sponsors issued

* DSC, DMC, DMSC

2006 US Food and Drug Administration Guidance Document



Guidance for Clinical Trial Sponsors

Establishment and Operation of Clinical Trial Data Monitoring Committees

For questions on the content of this guidance, contact the Office of Communication, Training, and Manufacturers Assistance (CBER) at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
March 2006

OMB Control No. 0910-0581
Expiration Date: 3/30/2009
See additional PRA statement in Section 8 of this guidance

http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

DSMB vs. CEC

DSMB also known as:

- Data Monitoring Committee (DMC)
- Monitors accumulating data from clinical trial , including unblinded data
- Decisions based on summary data

≠

Clinical Events Committee

- **Reviews individual events**
- **Adjudicates if event meets study definitions**
- **Always blinded**

Data and Safety Monitoring Boards
Roles and Responsibilities

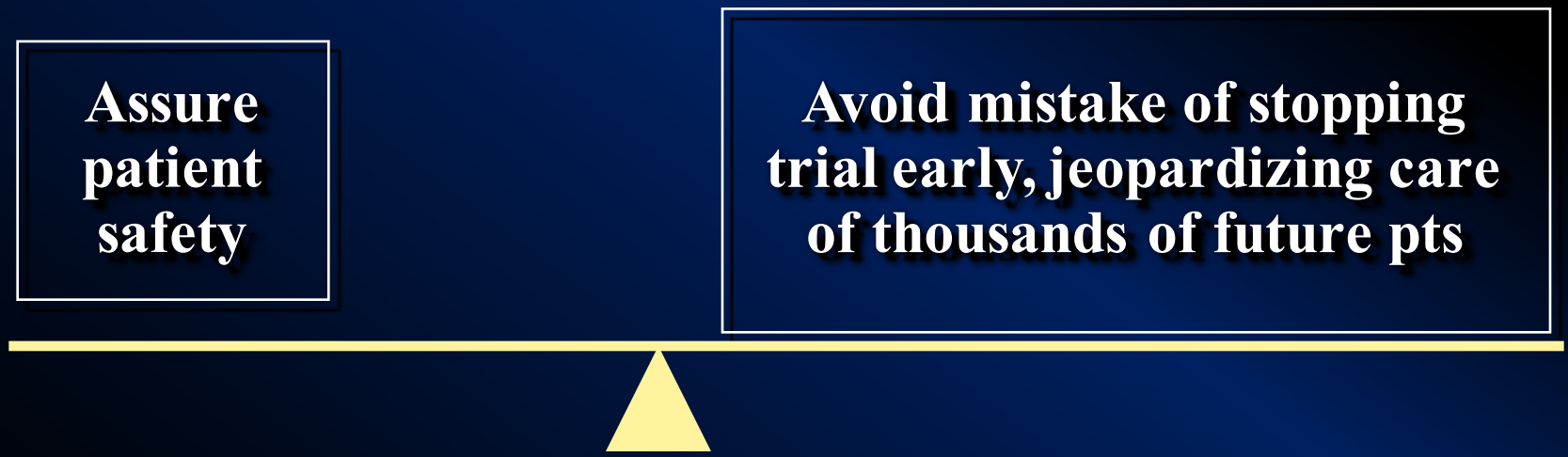
- An independent group of experts that advises the Steering Committee
- Reviews accumulating data from a clinical trial over a specified time interval
- *The overall responsibility of the DSMB is to protect the ethical and safety interests of subjects while protecting as much as possible the scientific validity of the study*
- Other monitoring responsibilities may be assigned for particular studies

Monitoring Requirements for Clinical Trials

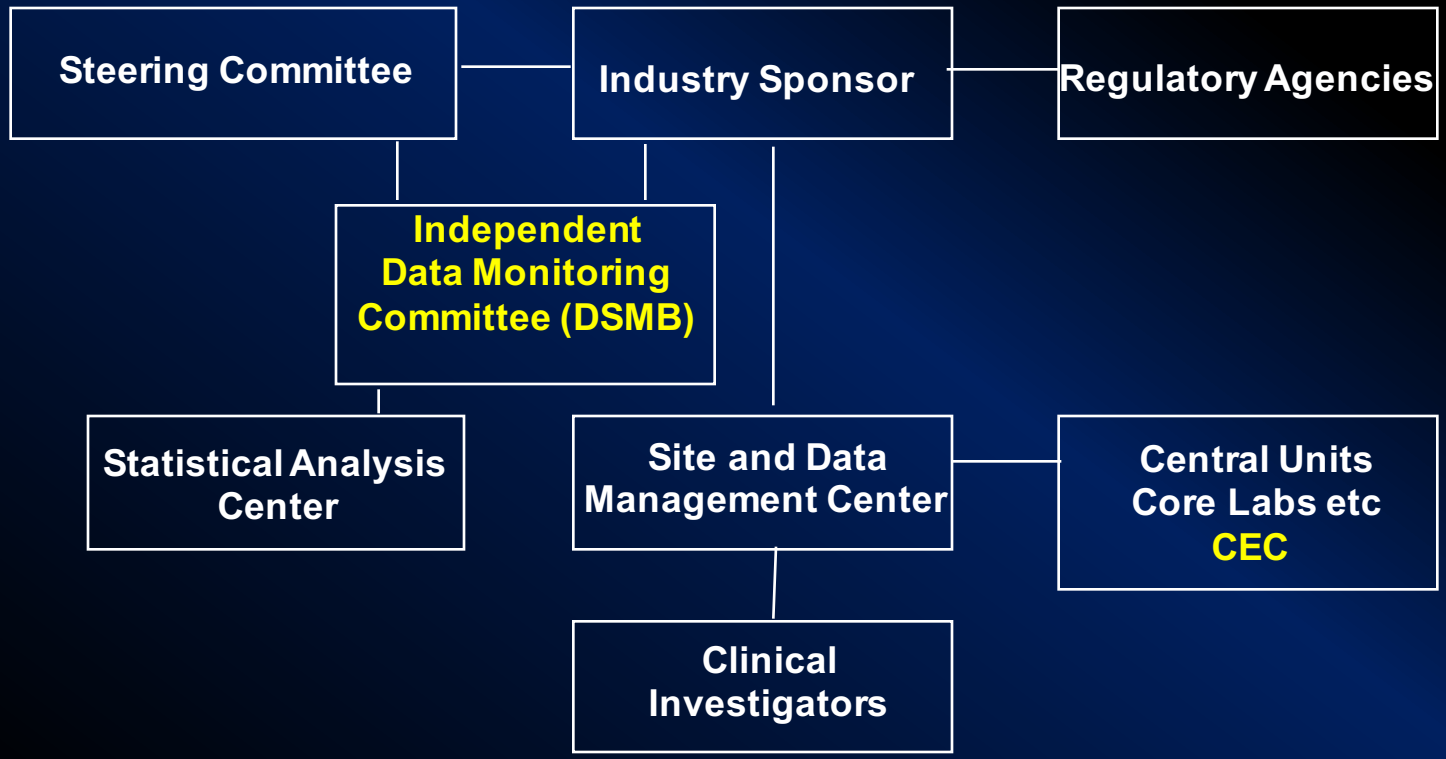
- Protect patient safety by assessing for harmful outcomes
- Evaluate protocol compliance, enrollment trends, data completeness and timeliness
- Test pre-trial assumptions (event rates, population characteristics)
- Evaluate treatment comparisons (interim analysis for efficacy)
- Ensure attainment of conclusive information to address the primary objective

Balancing Study Needs

Role of Data & Safety Monitoring Board



Clinical Trial Management Structure



Adapted from M. Fisher, E. Roecker, D. Demets.
Drug Inf J. 2001;35:115

When is a DSMB Needed?

- All studies require safety monitoring but not all require a formal DSMB
- DSMB recommended:
  - Increased risk to trial participants / safety concerns
  - Issues of possible scientific validity (interim analysis planned, possible trial modifications)
  - DSMB review is practical (long enough duration where DSMB will have impact)

Why an Independent DSMB?

- *Reduces bias – both real and perceived*
- Confidential data (including unblinded) required for DSMB to perform functions
- Any knowledge of unblinded data at the level of Sponsor, Investigators, trial management groups limits ability to manage the trial
- Protects trial stakeholders from difficult decisions for stopping/continuing trial
- Independence should extend to statistician/group preparing and reviewing the report

Specific roles of the DSMB

- Assess data quality
- Monitor recruitment and compliance
- Monitor safety (harm)
- Monitor efficacy (interim analysis)
- Decide on continuation / pausing / termination of trial
- Suggest additional analyses
- Advise on modifications of the protocol or sample size
- Consider ethical impact of decisions

Data and Safety Monitoring Boards
Membership of DSMB

- Membership should reflect disciplines necessary to interpret the data from the trial and to evaluate participant safety
- Generally consists of three to seven members including:
  - Expert(s) in the clinical aspects of the disease/patient population being studied
  - One or more biostatisticians, can include experts in clinical trial conduct and methodology
  - *Ad hoc* specialists may be invited to participate as non-voting members at any time (e.g. bioethicist)
  - Any individual with vested interests in the outcome of the study are <u>not</u> eligible to serve although they may attend open sessions

Data and Safety Monitoring Boards
Membership of DSMB

- Membership should reflect disciplines necessary to interpret the data from the trial and to evaluate participant safety
- The number of members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including:
  - Expert(s) in the clinical aspects of the disease/patient population being studied
  - One or more biostatisticians
  - Investigators with expertise in clinical trial conduct and methodology

Data and Safety Monitoring Boards
Conflict of Interest

- No member of the DSMB should have direct involvement in the conduct of the study
- No member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making
- At the beginning of every meeting, the Chair will reconfirm that no conflict of interest exists for members

Components of a DSMB Charter

- Purpose, Responsibilities
- Membership
  - Selection
  - Qualifications
  - Independence, conflicts
  - Remuneration
- Meetings
  - Format
  - Open session
  - Closed session
- Data reports
  - Independent statistician
  - Which data, locked?
  - Adjudicated?
- **Monitoring**
  - **Safety - timeliness**
  - **Efficacy - plan**
- **Membership**
  - **Selection**
- **Statistical considerations**
  - **Safety - ? Statistical guideline**
  - **Efficacy (state if no plan for early stopping)**
- **Report from DSMB - memo to Sponsor or delegate**
- **Sponsor response**
- **Disagreements**

Establish a Charter

- Introduction (trial objectives, inclusion, exclusion, sample size)
- Roles and responsibilities
- Initial review of protocol and charter
- DMC composition
- Relationships to PI, steering committee, sponsors
- Organization of meetings
- Confidentiality and communication
- Decision making (quality of data, interim analysis, stopping rules)
- Reporting
- Publication

DAMACLES Lancet 365:711 '05

Key Issues for Success

- Adequate data to make a decision (# events)
- Avoid stopping rules in non-inferiority trials
- Monitor over or under reporting of adverse outcomes (unadjudicated vs. adjudicated)
- Ensure trial enrollment is not too rapid or too slow
- Maintain confidentiality of data
- Avoid small group bias
- Avoid faulty initial study design
- Ensure careful analysis of composite endpoints

Monitoring Study Conduct

- Data Presented
  - Enrollment
  - Data Compliance and Timeliness
  - Protocol Deviations
  - Baseline characteristics
- Data usually reviewed in open session (may include Sponsor, investigators, CRO)
- Important safety and validity issues may be detected from study conduct data
- DSMB may recommend modifications or termination that impact the overall study or individual sites

Monitoring for Safety

- Data reviewed
  - Summary of adverse events
  - Summary of serious adverse events
  - Summary special adverse events of interest
  - Prespecified safety endpoints
  - Any individual events subject to expedited reporting or unblinding
- Safety reports must be dynamic and often submitted to all or part of DSMB outside of scheduled formal review meetings.
- DSMB may recommend modification or termination based on any perceived safety concerns or based on specified stopping guidelines.

Monitoring for Safety

Data related to subject safety and study risk

- Safety report
- Study validity (Will study be able to meet primary scientific objective? i.e. are subjects being exposed to risk with the opportunity to provide valid answer to research question)
  - Enrollment trends
  - Testing pre-trial assumptions (study power, appropriate target population)
  - Informal efficacy (benefit vs risk)

DSMB Statistical Issues

Monitoring for Safety

- There can be unlimited number of reviews or interim analyses of safety endpoints!
- Generally no alpha penalty
- Less statistical rigor for early stopping – may not require statistical significance
- Stopping guidelines may or may not be prespecified – in any case DSMB can recommend stopping for any perceived safety concern

Monitoring for Efficacy

- DSMB may be asked to review one or more formal interim analysis to evaluate the study treatment for
  - Overwhelming efficacy – requires formal statistical testing based on number of “looks” to determine level of certainty
  - Futility – to determine probability that the study could meet the pre-specified hypothesis if it continued to completion
    - A stop for futility $\Rightarrow$ end of new treatment!!

DSMB Statistical Issues

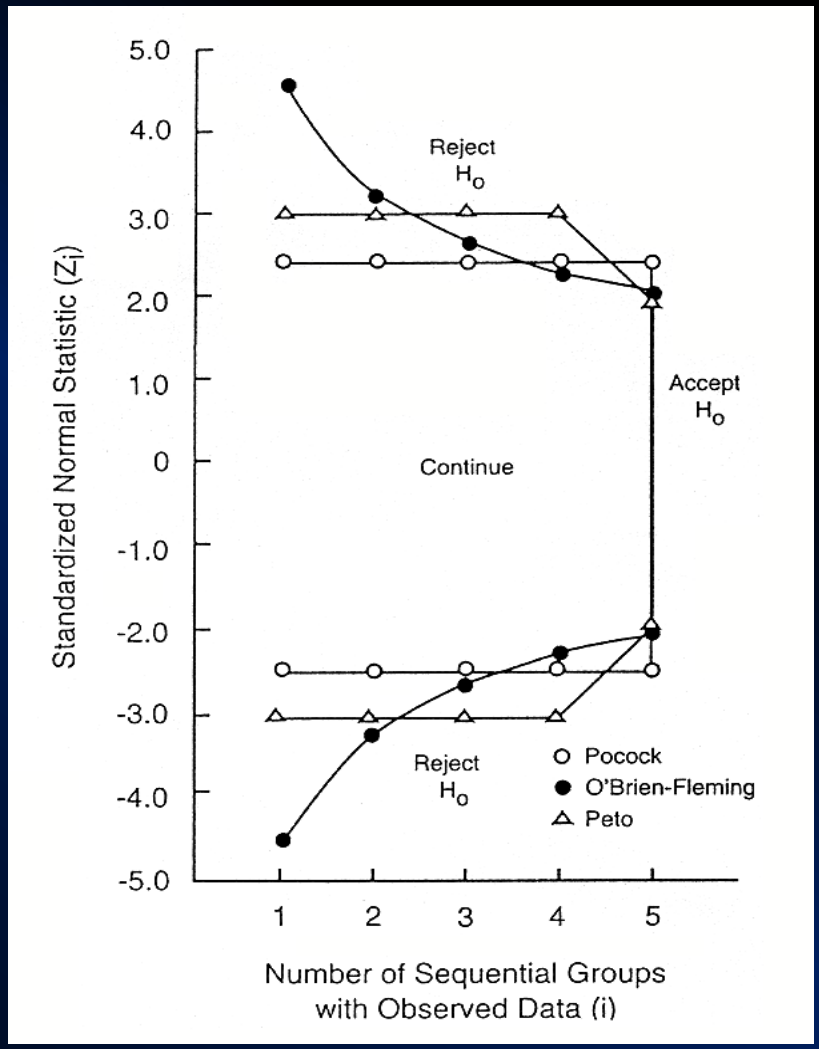
Monitoring for Efficacy

- The timing and number of formal interim analyses must be prespecified.
- The impact of an early comparison must be accounted for by adjustment of the p value (alpha spending)
- Balance the objectives of stopping early against the need to obtain adequate data for safety evaluation, secondary analyses, and avoid play of chance.

DSMB Decision Making Must be Individualized

- ⇨Statistical boundaries
- ⇨Internal consistency
- ⇨External consistency
- ⇨Risk/benefit ratio
- ⇨Current vs. future patients
- ⇨Clinical impact
- ⇨Public health impact

DSMC "Wisdom"



Modified from : http://www.nihtraining.com/

Independent DSMB
Early Stopping – Beyond Statistical Rules

Verify findings in the absence of real or *perceived* bias before trial termination —

- Are differences in harm related to prognostic differences between groups?
- Are there biases in patient selection, treatment, or evaluation of response variables?
- Is data compliance and adherence to protocol adequate to make the conclusions?
- Are apparent differences between treatments due to unusual experiences at 1 or 2 centers?

Statistical Guidelines ⇒ Ethical Needs

Individual Ethics:

is it OK to randomise the next patient?

Collective Ethics:

are we convinced what's best for future patients

in routine practice?

DSMB Statistical Issues

Monitoring for Efficacy

Stopping Rule – O'brien-Fleming

Interim Analysis	N	P value
1	1/3	0.001
2	2/3	0.0151
Final	All	0.0471

Stopping Guidelines for Efficacy (Superiority)

need proof beyond reasonable doubt

ie very strong evidence (eg Peto rule: P<.001)

stopping early ⇒ change in future practice

only a few interim looks for efficacy:

sometimes just one (or even none!)

Peto rule: simple, negligible statistical penalty

O'Brien and Fleming: too lenient at later looks

Statistical Guidelines for Harm

Primary endpoint (and all cause death?)

If pre-licencing:

more frequent looks

more lenient boundary, eg $P<.01$

If treatments in widespread use:

eg post-licencing safety trial

same guidelines as for efficacy (symmetry)

stop early $\Rightarrow$ change to common practice

unexpected safety issues (SAEs): multiplicity, tough

Data and Safety Monitoring Boards
Controversial things

- In STEEPLE (enoxaparin at 2 doses vs UFH for elective PCI) at a fourth interim analysis there were more deaths (9) in the 0.5mg/Kg enoxaparin arm, then in UFH (3) p=0.1477, or 0.75mg/Kg arm (p=0.026). And the low-dose arm was stopped
- Bleeding was reduced in both enoxaparin arms
- At the end of the trial, there was no difference in mortality: ENOX 0.5mg 1%, UFH 0.4%, ENOX 0.75mg 0.2% and death and MI were reduced by 9% in the low dose enoxaparin arm

Data and Safety Monitoring Boards
Good Actions

- In OASIS 6* 22 catheter thromboses noted (Fondaparinux vs UFH or placebo in STEMI). DSMB identified all in the fondaparinux group
- Investigators were informed of blinded event rates and hematologists were consulted at McMaster
- Investigators advised to add unfractionated heparin at time of catheterization
- Two more catheter thromboses with fondaparinux (in 496 patients) and no increase in bleeding. Trial continued showing reduction in mortality with fondaparinux

*OASIS 6 *JAMA* 2006

Stopping for Futility

- Stop early due to lack of efficacy
- One (or two) looks with substantial data
  - 1) Conditional Power, given results so far what's the chances of P<.05 at the end?
  - 2) Confidence Interval, does the CI already exclude the minimum clinically important benefit
- Remember:
  - Sponsors differ re: wish for futility boundary
  - A stop for futility $\Rightarrow$ end of new treatment

DSMB Conclusions

- Stopping a clinical trial not based on simple algorithm or “rule”; complex interaction of medical, ethical, statistics.
- Independent DSMB of experienced experts required.
- Interim results need to be considered in the context of all internal and external data, including prior clinical knowledge and current practice.
- Clinical trials performed to have impact on clinical practice. DSMB should ensure they are designed, conducted, and analyzed rigorously and ethically.

Role of the DSMC: Conclusions

- Patient safety oversight is mandatory in most human subject CV trials
- DSMC should be independent, multidisciplinary, and involved in drafting own charter
- Integration of DSMC needs with core trial ops must be functional and still preserve confidential content of DSMC discussions
- Statistical stopping rules for benefit or for cause are necessary but not sufficient for DSMC “wisdom” in oversight