

Why Monitor Data and Safety



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Learning Objectives

- ▶ Describe the types of studies which need a data safety and monitor plan (DSMP), and what the plan should accomplish
- ▶ Describe the types of studies which will likely require a data and safety monitoring board (DSMB).
- ▶ Describe the membership composition of a typical DSMB, who is eligible to serve and who is not.
- ▶ Be familiar with common terms used in discussions about DMSPs and DSMBs.

Human Subject Protection

“Concern for the interests of the subjects must always prevail over the interests of science and society” Ref: **Declaration of Helsinki, 1964, ... 2009**

- ▶ Quality of the science
- ▶ Training of scientists
- ▶ Weighing benefit vs. risk
- ▶ Safeguards for research subjects
- ▶ Rights of research subjects

Primum non nocere” - Hippocrates, 460-377 BC

Regulations and Guidance

The Documents of importance are:

- ▶ Belmont Report (1979)
- ▶ Nuremberg Code (1948)
- ▶ Declaration of Helsinki (1964 2009)
- ▶ ICH E6 Guideline for Good Clinical Practices
- ▶ ICH E9 Guideline for Statistical Principals
- ▶ DHHS Regulations (45 CFR 46 ...) 18Jun91
- ▶ FDA Regulations (21 CFR 50, 56, 312, 812 ...)
- ▶ FDA Guidance Documents

Background

- ▶ May 1999: Duke University failed to respond to requests for proper monitoring of human volunteer subjects – federal regulators temporarily suspended research;
- ▶ Sept. 1999: Univ. of Pennsylvania; an 18 year old died from drugs given as part of gene vector therapy study; Understated risks, protocol not followed and Conflict of Interest not disclosed
- ▶ June 2001: Johns Hopkins Univ.; a 24 year old died after receiving inhaled hexamethonium. Subject developed a cough and her condition deteriorated. She was admitted to ICU and lived one month. OHRP suspended all federally-funded research.

Phases of Clinical Research

	I	IIa	IIb	III	FDA	IV
Subjects	Healthy Normal	First time in Patients	Patients	Patients	Safety	Patients
Number	20-100	25-27	50-200	>300		>1000
Measure	Dosage, Kinetics, Safety , Equivalence	Dose range, MOA, Efficacy, Safety	Efficacy, Safety	Efficacy, Safety		R:B ratio, New uses Safety
Value	Kinetics, Dynamics	Proof of Concept	Confirm how drug works	Confirm use	Review period	PMS , Patent extension, Market expansion
Time (y)	1-1.5	1	1-1.5	3-6	2-3	1-5

Terms and Concepts

DSMP - Data & Safety Monitoring **Plan**

DMP - Data Monitoring **Plan**

DSMB - Data & Safety Monitoring **Board**

IDMC – Independent Data Monitoring **Committee**

DMB - Data Monitoring **Board**

SMEC - Safety and Monitoring Efficacy **Committee**

TEC - Treatment Effects **Committee**

TSC - Trial Steering **Committee**

EAC - Endpoint Assessment **Committee**

CEC - Clinical Expert **Committee**

IRB – Independent / Institutional Review Board

Data & Safety Monitoring Plans



DSMPs / DMPs

- ▶ **What are they?**
- ▶ **Who creates them?**
- ▶ **Who is responsible for them?**
- ▶ **What is their function?**

Data & Safety Monitoring

Sponsors of studies evaluating new drugs, biologics, and devices are required to monitor these studies

Ref: **21 CFR 312.50, 312.56** drugs

Ref: **21 CFR 812.40, 812.46** devices

The monitoring plan is considered a critical component of the study protocol.

Ref: **21 CFR 312.23(a)(6)(iii)(g), 312.41(a)** drugs

Ref: **21 CFR 812.150(b)(10)** devices

Data & Safety Monitoring

The activity of reviewing the data collected with the goal of protecting the:

- ▶ Safety of the Participants.
- ▶ Credibility of the trial.
- ▶ Validity of the data.

The ethical conduct of research involving human subjects depends upon the assurance of the above

Safety Monitoring Plan - Purpose

Ensure the safety of all participating subjects to the greatest extent possible.

- ▶ Plan the on-going oversight and monitoring of the conduct of the study to ensure the validity and integrity of the data produced.
- ▶ Document the conditions and monitoring frequency regarding the decision as to whether or not the study should continue or be stopped.
- ▶ Specify the responsibilities (charter) of the DSMB (if a DSMB is required) or a TEC.

DSMP - Purpose

Stated another way, the Plan:

- ▶ Is to assure the safety of human subjects participating in clinical trials
- ▶ Is to assist in maintaining compliance with the study protocol specially in regards to safety matters and concerns.
- ▶ To identify opportunities for policy, procedure, or system changes

Content of a DSMP

All monitoring plans must include a description of the reporting mechanisms of AEs to the IRB, the Sponsor / NIH, and the FDA.

- ▶ Investigators must ensure that the Sponsor / NIH is informed of actions, if any, taken by the IRB as a result of its continuing review.
- ▶ The reporting requirement to the Sponsor / NIH may range from individual adverse event reports to summary reports from the monitoring group. In specific cases, the PI might be required to submit AE reports directly to the Sponsor

Content of a DSMP

The minimum required DSMP content includes the following information:

- ▶ Who will be responsible for monitoring?
- ▶ What data will be monitored consistent with the protocol?
- ▶ What process will be used to collect data in the monitoring process?
- ▶ Specifically, the Adverse Event (AE & SAE) monitoring plan is to be clearly outlined

More Content of a DSMP

The DSMP must define the following items:

- ▶ Characteristics of the trial subject population
- ▶ The safety endpoints and how they are assessed
- ▶ Listing of expected Events / background AEs
- ▶ Who reviews the Safety Data
- ▶ Criteria for study discontinuation
- ▶ Need, or not, for a DSMB
- ▶ Identity of the Medical Monitor (if there is one)

SMP - Review all Safety Data

The SMP must describe the data to be reviewed:

- ▶ All Adverse Events (AEs) including by subject
- ▶ Listing of SAEs, deaths, subject withdrawals
- ▶ Laboratory tests done including by subject
- ▶ All concomitant medications taken by subjects
- ▶ All Ad hoc reports
 - ✓ Telephone reports
 - ✓ Conference call reports
 - ✓ Meeting minutes

Studies Requiring a DSMP

All studies utilizing human volunteer subjects as study participants require a written plan as to how the experimental data and SP safety information is to be monitored (i.e. a DSMP / SMP).

All FDA and NIH clinical studies require a formal DSMP whether or not a DSMB / DMC is to be required.

When the DSMB meets and how they function (Charter of the DSMB) is determined in the DSMP of the protocol.

Monitoring Data & Safety

When to discontinue a study – one of the main functions of a DSMP is to Establish “stopping rules”:

- Clear evidence of harm or harmful AE's
- No likelihood of demonstrating benefit
- Overwhelming evidence of benefit

i.e. Subject Safety under the microscope

- ▶ Data & Safety Monitoring Plans (DMP, DSMP)
- ▶ Data & Safety Monitoring Committee (IDMC, DSMB)

Types of “Stopping Rules”

There are categories of the rules that would stop a large study, or one complicated enough to have a DSMB. In general they are of two types:

- ▶ **Safety Rules** - these may be AE specific and might be expressed as a statistic contrasting *event rates* between treatment and control groups
- ▶ **Efficacy rules** – Use to allow a conclusion to be drawn concerning the main trial question as soon as sufficient data are available. This could be ‘effect’ or ‘lack of effect’

DSMB can override stopping rules

Data & Safety Monitoring Boards



DSMBs / DMCs

- ▶ **What are they?**
- ▶ **Reasons to have a DSMB?**
- ▶ **Who creates them?**
- ▶ **Who is responsible for them?**
- ▶ **What is their function?**

A Clear Definition

A Data and Safety Monitoring Board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor for stopping the trial for efficacy, for harms, or for futility

FDA Guidance

The definition and activities of a DSMB / DMC :

- ▶ A DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial.
- ▶ The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial

Ref: FDA Guidance on Safety Monitoring

Reasons for a DSMB, DMC

Ethics

- ▶ Oversight to insure subject / patient safety
- ▶ To be able to quickly react to untoward events

Insurance

- ▶ Oversight of study conduct progress
- ▶ Insure that the study is on track to achieve basic objectives
- ▶ Early warning of operational matters requiring a stopping of the study (safety, +/- efficacy)

Reason - Vulnerability

To safeguard the interests of patients /study participants - with special vigilance to:

- ▶ Pediatric population
- ▶ Life-threatening diseases - e.g. cancer, HIV
- ▶ Emergency treatments - e.g. ACLS interventions
- ▶ Psychiatric patients unable to consent
- ▶ Persons in poverty - monetary coercion
- ▶ Pregnancy - to protect the unborn
- ▶ The elderly

Regulatory Requirements

Sponsors are required to monitor (for safety) studies evaluating new drugs, biologics, & devices

- ▶ 21 CFR 312.50, 312.56 for drugs
- ▶ 21 CFR 600.80 for biologics
- ▶ 21 CFR 812.40 and 812.46 for devices

Current FDA regulations impose no requirements for the use of DSMB/DMC in trials except for research studies in emergency settings. *Why?*

Ref: 21 CFR 50.24(a)(7)(iv)

Other Oversight Committees

Several different groups may assume or share responsibility for various aspects of clinical trial monitoring and oversight

- ▶ Institutional Review Boards
- ▶ Clinical Trial Steering Committee
- ▶ Endpoint Assessment / Adjudication Committee
- ▶ Site / Clinical Monitoring
- ▶ Others with Monitoring Responsibilities
 - The Investigator - front line responsibility
 - The Sponsor - send to the FDA relevant data
 - The FDA - review the data in a timely manner

The NIH view of the DSMB Charter

The DSMP spells out how the DSMB will function in what is called the ‘Charter’ of the DSMB. This will include the following:

- ▶ Duties and responsibilities of the Board
- ▶ Composition / Membership of the Board
- ▶ Organization / form of the meetings
- ▶ The form and nature of documentation / decisions
- ▶ A statement regarding confidentiality*
- ▶ The role post-trial

Ref: www.niams.nih.gov/rtac/clinical/DSMBCharter.htm

Charter Components Spelled Out

The ‘Charter’ of the DSMB components:

- ▶ Responsibilities
- ▶ List of members and credentials
- ▶ List of Conflict of Interest minimization rules
- ▶ Meeting frequency and format
- ▶ The methods or organization of the data etc.
- ▶ Methods, timing and voting of data reviews
- ▶ Description of the documentation of the meetings
- ▶ A statement of the impact to the study

DSMB Charter May Include

Sponsors of well-controlled studies should take appropriate measures to minimize bias.

- ▶ This should include written procedures, which may be in the DSMB charter, to ensure the minimization of bias, such as maintaining confidentiality of the interim data.

Ref: **21 CFR 314.126(b)(5)** - drugs

Ref: **21 CFR 860.7(f)(1)** - devices

An Increase in number of DSMBs

The increasing use of DSMBs in industry sponsored trials is the result of:

- ▶ A growing number of industry-sponsored trials with mortality or major morbidity endpoints
- ▶ An increasing collaboration between industry and the government
- ▶ An increased awareness within the scientific community of clinical trial conduct issues and analysis subject to bias
- ▶ Concerns of IRBs regarding ongoing trial monitoring and subject / patient safety in multicenter trials

DSMB Roles / Recommendations

With the understanding that role is “Advisory”

- ▶ Major role is to preserve the integrity of the trial
- ▶ Review the protocol, trial progress, data quality
- ▶ Assess safety at all levels of a study
- ▶ Assess efficacy and futility
- ▶ Assess sample size assumptions / impact
- ▶ Recommend to continue as planned, temporary stop until an issue is solved, modifications to the protocol, or even early termination

Function of a DSMB / IDMC

- ▶ Review the protocol, IB, ICF, and DSMP
- ▶ Review AE's, SAE's, Dropouts, symptoms, lab results, statistical evidence, and subject demographics by site and treatment group
- ▶ Review new information from other or similar studies using the same therapy
- ▶ Evaluate the progress of the trial
- ▶ Conduct interim analysis of trial data
- ▶ Ensure confidentiality of trial data

Function of a DSMB

One of the main functions is to maintain trial integrity, which may be compromised if those knowing ongoing results have the ability to make changes in the protocol

- ▶ Recommendations to change the inclusion criteria, the trial endpoints, or the size of the trial are best made by those without knowledge of the accumulating data - except in certain emerging safety concern situations

Confidentiality of Interim Data

Interim data, whether treatment assignment is revealed or blinded, will be most securely protected from inadvertent or inappropriate access by the sponsor or project team:

- ▶ Procedures should be established to safeguard confidential interim data from the project team, investigators, sponsor representatives, or anyone else outside the DSMB & the statistician

Ref: **21 CFR 314.126(b)(5)** - drugs

Ref: **21 CFR 860.7(f)(1)** - devices

DSMB Statistical (IA) methods

When a DMC looks at interim data, p-value adjustments are necessary, therefore

- ▶ Avoid over reaction to 'early' trends by using a more strict stopping rule e.g. $\alpha = 0.001$ (depends on the alpha spending technique used and the number of interim analysis planned)
- ▶ The key is to maintain alpha level of 0.05 for the final / last analysis of the data

Your friendly statistician is an essential component of this process

DSMB / DMC Statisticians

There are three types of statisticians involved in the DSMB process:

- ▶ **DSMB members**, which may be more than one, are unblinded when necessary, and do not see electronic data or perform analysis.
- ▶ **Protocol statistician** who remain blinded and not involved in the DSMB report
- ▶ **Independent statistician** who is unblinded, prepares the reports (open and closed) and presents the results at the DSMB meetings

Inflation of Type I Error

If interim analysis utilizes α levels of 0.05 at each look, statistical theory and simulations have shown that the final alpha level could be approx. 20% (chance of false positive result is 4 out of 20)

- ▶ Analysis # 2 Type I error = .0831
- ▶ Analysis # 3 Type I error = .1073
- ▶ Analysis # 4 Type I error = .1262
- ▶ Analysis # 5 Type I error = .1417
-
- ▶ Analysis #10 Type I error = .1934

Avoid Administrative Analyses

It is not recommended to;

- ▶ Look at data if no intent to modify the study
- ▶ Look at data for 'insurance' issues
- ▶ Assume that there would be no adjustment of 'p-value' as there was no intent to make changes
- ▶ Assume an adjustment in the study is needed if efficacy data suggest a trend (overacting to early trends)

Two other errors seen

Using a DSMB/DMC for safety reasons only

- ▶ The DMC needs access to both efficacy and safety to assess risk and benefit

Blinding of DSMB/DMC members

- ▶ Imposed by some sponsors supposedly to prevent bias and to avoid early trend changes

Blinding not FDA or ICH mandated - in fact:

- ▶ ICH E9 4.1 “Interim analysis requires unblinded access to treatment group assignments.
- ▶ ICH E9 4.5 “Interim ... unblinded data & results”

The DSMB/DMC - IRB connection

The activity of reviewing the data collected with the goal of protecting the safety of the study participants is also the purview of the IRB.

- ▶ The individual Investigators (or the sponsor of the investigational device) are responsible for assuring that IRB's are made aware of *all / any* significant new information that arises about a clinical trial

Ref: **21 CFR 56.103, 312.66** - drugs

Ref: **21 CFR 812.40, 812.150(a)** - devices

The DSMB/DMC - IRB connection

IRBs are charged to determine whether risks to subjects are minimized by “using procedures which are consistent with sound research design”

Ref: 21 CFR 56.111(a)(1)(i)

- ▶ The IRB may request the approach to trial monitoring, including the stats basis for early termination, when relevant, and what steps the sponsor is taking to minimize the risks to patients
- ▶ They might ask if a DSMB is established

Need For a DSMB / DMC

The activity of reviewing the data collected with the goal of protecting the:

- ▶ Safety of the study participants by continuous assessments .
- ▶ Credibility of the trial.
- ▶ Scientific Validity of the study and the data emanating from the trail

Regarding Risk

Reasons to establish a DSMB:

- ▶ The study endpoint is one for which an early result might ethically require early termination of the study
- ▶ There a reason for a particular safety concern such as when the procedure to administer is invasive
- ▶ The treatment or device to be tested novel*
- ▶ The study population is potentially fragile or vulnerable
- ▶ Prior information suggests the possibility of serious toxicity
- ▶ Is the trial large, of long duration, or multicenter?

Regarding Device Risk

Medical Devices are *classified* according to risk into three classes:

- ▶ Class I - Low Risk

- ✓ Eg: Elastic Bandages,

- ▶ Class II Moderate Risk

- ✓ Eg Powered wheelchairs, Hemostatic bandages

- ▶ Class III Highest Risk

- ✓ Eg Coronary stent, Heart valves

Regarding Scientific Validity

Reasons to establish a DSMB also include the *perception* of scientific validity:

- ▶ Time may affect disease understanding, the trial population, or treatment standards
- ▶ When there may be a reason to modify inclusion criteria, trial endpoints, trial size without the knowledge of the sponsor or study staff of the reasons

When trial organizers review interim data, they now have compromised any semblance of objectivity even if no changes are made

Studies Usually Requiring a DSMB

- ▶ High profile / pivotal trials (↑ impact on practice)
- ▶ Survival as the outcome measurement
- ▶ Studies with unknown or greater than minimal risk
- ▶ Large multi-center / site Phase III & IV studies
- ▶ Long duration / long term Studies
 - Eg: Long term Multi-centered studies
- ▶ Studies with large patient numbers
- ▶ Large blinded trails
- ▶ Studies in vulnerable populations

Data & Safety Monitoring Boards



DSMBs / DMCs

- ▶ **What is their size?**
- ▶ **Composition of a DSMB?**
- ▶ **Selection of members?**
- ▶ **Conflicts of Interest**
- ▶ **Meetings**
- ▶ **Reports**

DSMB / DMC - Size

Minimum size: 3

- ▶ 2 clinicians (1 expert in the condition under study)
- ▶ 1 biostatistician

Typical size: 5

- ▶ 2 clinicians (1 specialist in the condition)
- ▶ 1 biostatistician
- ▶ 1 ethicist
- ▶ 1 reporting secretary

Maximum size: 10

- ▶ The above plus specialists in area of likely AEs, UADEs, therapeutic endpoint, etc.

DSMB - Composition

Prior DSMB experience is of value, appropriate gender / ethnic representation, and:

- ▶ Clinicians with expertise in relevant specialty
- ▶ Biostatisticians with clinical trial knowledge
- ▶ Medical ethicists knowledgeable about clinical res.
- ▶ As needed
 - Clinical Pharmacologist
 - Toxicologist
 - Epidemiologist
 - Laboratory Scientist / engineer
- ▶ Lay person with study population expertise

DSMB Member Selection Criteria

The decision as to who should be invited to fill the DSMB varies with the exception of:

- ▶ Physicians with relevant expertise
- ▶ Statistician with clinical trial experience
- ▶ Persons with Clinical Trial experience
- ▶ Previous experience on a DSMB

They all must be free from or lack a significant Conflict of Interest

DSMB Member Selection Criteria

Those who may not be selected

- ▶ Members of the Company, the Sponsor, or clients of either
- ▶ An Investigator who is participating in the trial
- ▶ The Investigators contact: company / sponsor
- ▶ Any individual who can influence the subject / patient recruitment process
- ▶ Individuals w data classification responsibilities
- ▶ Individuals who can influence the design, objectives, or analysis of the study

Conflict of Interest (COI)

Special consideration of COI in choosing members so that at full disclosure members:

- ▶ Are free of financial interests that could affect the outcome of the trial
- ▶ Are not Investigators who enter subjects
- ▶ Do not have strong views regarding the trial and the intervention -i.e. An intellectual COI
- ▶ Have no relationship with the leadership of the trial. (partner in practice, department colleague ..)

DSMB / DMC Composition

The most important issue about the composition of the DSMB is not the number of members but the ethics, honesty, and that all members are totally and absolutely free from any “Conflict of Interest”.

No one on a DSMB may have any connection with the agent being tested.

'Conflict of Interest' Defined ?

- ▶ A conflict of interest is any financial incentive, which would cause an investigator to lose their objectivity (or create the appearance thereof) in the design, conduct, or reporting of research, which, in turn, compromises scientific integrity and / or negatively impacts the public trust
- ▶ Conflicts of interest in clinical research are all about money, power, greed, and ego where the interests of the sponsor / investigator come first at the expense of the subject and then the public

COI Stated another way:

A ‘conflict of interest’ (COI) is anything, be it personal, financial, academic, religious, or political, “which, when revealed at a later time, would make a reasonable reader feel misled or deceived”.

- ▶ A COI is a financial or personal relationship that influences (biases) actions of the individual
- ▶ The potential for a COI can exist whether or not an individual believes that the relationship in question affects her / his scientific judgment

The Dilemma ?

Regarding conflicts of interest it must be kept in mind that :

- ▶ Appearance of a conflict can be as important as the reality
- ▶ Appearance can undermine trust as surely as would the reality
- ▶ Institutions, in addition to, and not just individuals are subject to 'conflicts of interest'

DSMB Meetings

There may be both open and closed meetings or combinations

- ▶ **Open session** where a blinded presentation is made by the study chair or the statistician
- ▶ **Closed session** often presented by the independent statistician and where the unblinded results are discussed and possibly recommendations made

DSMB Open Meetings

Those in attendance may be from the sponsor, the PI, the steering committee, the FDA, etc

An “Open Session” is where information is discussed that is non-confidential and blinded.

- ▶ Recruitment status,
- ▶ Baseline characteristics,
- ▶ Ineligibility rate,
- ▶ Protocol deviations (number and extent),
- ▶ Administrative data, etc
- ▶ External data from the sponsor re safety

What is in a DSMB Report

A report, signed by the chair, has one of the following general recommendations:

- ▶ Study to continue as it is presently conducted
- ▶ Study continues with the following modifications: ... which are to become amendments:
- ▶ Study must stop due to the following concerns: ... and those patients currently under treatment should: ...
- ▶ Study is to cease as per the 'stopping rule' formulated in the Charter of this DSMB which is: ...

A Typical DSMB Report

A report, signed by the chair, could be like the following - appropriate check boxes:

- The trial to continue without change
- The trial protocol / plan should be modified as follows:
- The trial should be terminated due to:
 - Serious concerns about subject safety
 - Serious concerns about the safety of the device
 - Benefits do not outweigh the risks to subjects
 - Trial outcomes do not justify risk
 - New developments impact subject safety/ethics
 - Unreasonable degree of difficulty of procedures

DSMB / IDMC Must Know ...

The key reason for unblinded monitoring to assess the risks and benefits is patient safety

- ▶ A DSMB is an Independent group with absolutely no conflicts of interest
- ▶ A DSMB has no vested interest in study results
- ▶ A DSMB makes no decisions
- ▶ The DSMB charter describes the empowerment roles, boundaries, and responsibilities involved

Being unblinded is essential

References

Selected references:

- ▶ Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. March 2006
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- ▶ DSMB Charter
www.niams.nih.gov/rtac/clinical/DSMBCharter.htm
- ▶ www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf

Thank you.

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Planned Future Webinars

- ▶ Study Conduct Documentation to assure a good Audit
- ▶ How Does 21 CFR Part 11 Help Ensure Data Integrity and Subject Safety
- ▶ Investigator Responsibilities in Research Involving Human Subjects: The ICH View / Position
- ▶ Investigator's responsibilities and Legal commitment's in Clinical Research affects Study Conduct - FDA View
- ▶ Recruiting is Vital to Success in Clinical Research
- ▶ Role of Drug Induced Liver Injury in the Process
- ▶ What is the Role of Data & Safety Monitoring in

My Associations



FCP



CPI