Planning for Your Plan: Data and Safety Monitoring Plan Development & Implementation

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Learning Objectives

• Describe the purpose of a data and safety monitoring plan
• Identify responsible parties for developing and implementing a data and safety monitoring plan
• Summarize different types of data and safety monitoring and how to develop appropriate plans based on the nature of the study
• Describe best practices for implementing a data and safety monitoring plan
Disclaimer

- Can’t cover everything
- Not everything may apply but **THINK** about how you can apply concepts indirectly
DEFINITIONS

(OHSP POLICIES 506 & 801)

**PAY ATTENTION TO YOUR PROTOCOL**
Data & Safety Monitoring

The process for reviewing cumulative data throughout an ongoing study to ensure:

• Safety of the study subjects; &
• Continued validity and scientific merit

→ Generally applies to ALL studies

(OHSP Policy #01 – Reporting Research Events)
Data & Safety Monitoring *PLAN* (DSMP)

A written plan outlining the appropriate oversight and monitoring of the conduct and progress of the study to:

- Ensure that important information that may affect the safety or welfare of subjects is collected, recognized and acted upon as quickly as possible; &
- Ensure the validity and integrity of the research data
Data & Safety Monitoring **PLAN**

• Required for all research posing greater than minimal risk
• May be required for selected studies involving minimal risk
Data & Safety Monitoring BOARD (DSMB)

A formal committee of qualified individuals with relevant subject-matter expertise and who do not have any conflicts of interest with the research established to:

- Review interim data to assess both safety and efficacy; &
- Issue recommendations regarding the continuation, modification or termination of the study
Data & Safety Monitoring **BOARD**

- May include experts in the field, laboratory scientists, statisticians, ethicists, subject advocates, etc.
- May be independent or may include individuals involved in the research
- AKA (For the Purposes of Today’s Presentation): Data & Safety Monitoring Committee, Data Monitoring Committee, Safety Monitoring Committee, Event Monitoring Committee
Safety Monitor

A qualified professional with relevant subject-matter expertise whose primary responsibility is to provide periodic safety monitoring throughout the conduct of the study.

• May be independent or may be an individual responsible for conducting the study
Adverse Event

Any undesirable and unintended (although not necessarily unexpected) effect occurring as a result of interventions, interactions, or collection of identifiable private information in research. In medical research, any untoward physical or psychological occurrence in research, including abnormal laboratory finding or newly identified or worsening symptom(s) or disease(s) that occurs during the conduct of a research study.

• AKA (For the Purposes of Today’s Presentation): Adverse Experience, Adverse Reaction, Adverse Device Effects, Research Events
BASIC RESPONSIBILITIES
PI: Single Center Study

DSMP-Related Responsibilities:
• Develop DSMP
• Ensure the activities of the DSMP are carried out
  ➔ Do it, Document it & Report it!
PI(s): Multi Center Study

### Lead PI

**DSMP-Related Responsibilities:**
- Develop DSMP
- Ensure the activities of the DSMP are carried out
  - Do it, Document it & Report it!

### Site PI

**DSMP-Related Responsibilities:**
- Ensure the activities of the DSMP at the site-level are carried out
  - Do it, Document it & Report it!
  - Monitor subject status
Institutional Review Board

IRB

DSMP-Related Responsibilities:
• Review for appropriateness
• Ensure consistency with Criteria for Approval (45 CFR 46.111 & 21 CFR 56.111)
• Continued review

** Note that, per OHSP Policy, the Scientific Reviewer is also responsible for reviewing the plan and ensuring appropriateness/adequacy
Monitoring Body

DSMP-Related Responsibilities:
• Ensure the activities of the DSMP are carried out
  ➔ Do it, Document it & Report it!

Monitoring Body

Clinical Monitor  Safety Monitor  DSMB  Sponsor Monitoring  Steering Committee
DSMP DEVELOPMENT
Protocol Complexity

Very Simple
- Survey/Focus Groups
- MR Observational
- Data/Specimen Repository

DSMP

Very Complicated
- Drug/Device Study
- Study with IND/IDE
- Multi-Site Study

IND = Investigational New Drug
IDE = Investigation Device Exemption
DSMP Complexity

Very Simple
- Investigator Monitoring
- Investigator Monitoring & Safety Monitor

DSMB
- DSMB & Safety Monitor

Very Complicated
- DSMB, Safety Monitor Plus
DSMP Development

• Tailor DSMP to nature, size, and complexity of:
  – Research protocol
    ➢ Extent of prior human experience
    ➢ Early (I/II) vs. late (III) phase
    ➢ Complexity
    ➢ FDA approval
    ➢ Blinding
  – Expected risks of the research
  – Subject population

(OHSP Policy 506; FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, 2006)

Cartoonist: Don Mayne (www.researchcartoons.com)
DSMP Development

• Tailored plans are **KEY**!
  – Insufficient DSMPs = increased risks to subjects
  – Excessive DSMPs may:
    ➢ Run inefficiently, thereby increasing risk to subjects
    ➢ Set up study teams for compliance problems

• **THINK** about the Who, What, When & How
DSMP: At a Minimum

• DSMP should include:
  1) The individual(s) responsible for monitoring

Examples: OHSP Policy 506 & NIH Policy for Data and Safety Monitoring
DSMP: At a Minimum

• DSMP should include:
  
  1) The individual(s) responsible for monitoring
     - Experts in all scientific disciplines needed to interpret the data and ensure patient safety
     - May require ad hoc specialists as needed
     - Free of conflicts of interest
     - Independence?

(OHSP Policy 506; FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, 2006; National Institute of Dental and Craniofacial Research Data and Safety Monitoring Board Guidelines, 2014)
DSMP: At a Minimum

- DSMP should include:

  2) The process for conducting the monitoring

  - Reviews prior to study initiation?
    - Protocol & DSMP: e.g., Reporting requirements, stopping guidelines, unblinding procedures, events that might trigger an unscheduled review

  - Reviews during the study?
    - Data related to efficacy or effectiveness (per pre-established statistical guidelines)
    - Data related to subject safety (cumulative data & individual events of concern)

(OHSP Policy 506; FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, 2006; National Institute of Dental and Craniofacial Research Data and Safety Monitoring Board Guidelines, 2014)
DSMP: At a Minimum

- DSMP should include:

  2) The process for conducting the monitoring
      - Reviews during the study? (Continued)
        - Study conduct: e.g., recruitment & retention; data quality, completeness & timeliness; site performance; etc.
        - External data
      - Timing of reviews?
      - How review will be conducted?
      - Recommendations?
        - Continue with out change, modification, or termination

(ODSP Policy 506; FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, 2006; National Institute of Dental and Craniofacial Research Data and Safety Monitoring Board Guidelines, 2014)
DSMP Drivers

• Protocol
  – Eligibility criteria that help ensure appropriate risk/benefit ratio
  – Safety evaluations at appropriate intervals
  – Provisions to stop or modify treatment or intervention due to:
    • adverse events
    • disease progression
    • need for additional/alternative therapy

• Protocol and/or other plans:
  – Data Management Plan including data submission timeline
  – Site/Clinical Monitoring Plan including frequency and type of site monitoring
  – Statistical Analysis Plan including justification of sample size and any planned analyses (e.g., safety, efficacy)
DSMP: At a Minimum

- DSMP should include:
  3) The mechanism for documenting the monitoring
     - Summary of what was reviewed
     - Findings, overall safety assessment & recommendations (with rationale included as appropriate)
  4) Who will be notified of any monitoring activity outcomes
     - Study sites, IRBs, sponsors, regulatory agencies, etc.

(OHSP Policy 506; FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, 2006; National Institute of Dental and Craniofacial Research Data and Safety Monitoring Board Guidelines, 2014)
DSMP: At a Minimum

• DSMP should include:
  1) The individual(s) responsible for monitoring
  2) The process for conducting the monitoring
  3) The mechanism for documenting the monitoring
  4) Who will be notified of any monitoring activity outcomes

• One more thing to consider...

Is the DSMP practical?
Your poll will show here

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Case Study #1

- Prospective, randomized, controlled study comparing restrictive v. liberal transfusion strategies (current practice varies widely & historical recommendations are not evidence-based)
  - Low: Transfused when Hgb below 7.0g/dL or 9.0g/dL (depending on type of surgery)
  - High: Transfused when Hgb below 9.5g/dL or 12g/dL (depending on type of surgery)
  - PICU attending & surgeon have discretion to transfuse subjects per their clinical judgment, regardless of assignment
- Enrolling neonates and infants ≤ 10kg undergoing surgery for CHD
- 2 small study-related blood draws (through catheter), all other tx = standard care
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Case Study #1

• Independent Medical Safety Monitor
  – Interim review of safety data every 6 months
  – Review each subject death to determine expectedness & relatedness (SM notified within 24 hours)
  – Review of interim statistical analysis

• Safety Reports: info on all SAEs, other AEs, laboratory test results & recruitment/retention data

• SM must have expertise in particular events of importance (e.g., cardiogenic & hypovolemic shock)

• Parameters for terminating the study
Case Study #2

- Randomized, placebo-controlled multi-center phase III trial of nutritional supplement to slow down XYZ disease progression (vulnerable population)

- Participation includes:
  - Safety labs
  - Disease progression monitoring
  - Questionnaires
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Case Study #2

- Blinded clinical safety monitor reviews aggregate safety data on monthly basis and safety events in real time
- DSMB
- Study Steering Committee
- Interim safety, efficacy & futility analysis
Case Study #3

- Multi-Site, prospective, double-blind, randomized, controlled study to assess the safety & efficacy of a computer-based cognitive treatment program versus a computer-based control
- Enrolling adults diagnosed with schizophrenia
  - Must demonstrate adequate decisional capacity
  - Clinically stable for 8 wks prior to consent
  - Maintained stable tx with antipsychotics and/or other concomitant psychotropic tx for at least 6 wks prior to consent
- Complete defined number of computer-based sessions over the course of the tx period
- Evaluated at baseline, mid-way & end of tx phase
  - Cognitive, life-skills, general health assessments
  - Assessments specific to dx, monitoring of schizophrenia
  - Suicide severity scale
Your poll will show here

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Case Study #3

- Data Monitoring Committee
  - Review safety data, aggregate study data, data management, and a priori analyses of primary & secondary endpoints
- Blinded, independent psychometrician monitors neuropsychological assessments
- Remote/in-person data monitoring to review accuracy & integrity of the data
Appendix 1

Recommended Safety Evaluation Criteria

Investigator (or appropriate study team designee) monitoring only:
This level of monitoring would be appropriate for minimal risk studies and certain single-site greater than minimal risk studies. The prompt reporting of reportable events and other study-related safety information is made to the RSRB, sponsor, federal agencies, and another other required entities as outlined in the approved protocol. Protocol deviations that involve a safety issue and proposed amendments are reported by the Investigator. Examples of study activities appropriate to this level of review:

- Open-label, single-site clinical trials
- Small pilot studies with drugs/devices
- Phase 4 drug or device studies

Investigator monitoring and independent safety monitor:
The Investigator monitors the study as noted above, with additional oversight by an independent safety monitor. This individual has appropriate clinical and research expertise and should have no conflicts in monitoring the study. This level of monitoring would be appropriate for studies posing greater than minimal risk that may require independent oversight. Examples of study activities appropriate to this level of review:

- Phase 1 or 2 single-site studies
- Investigator-initiated study involving potential undue influence in a vulnerable population

Investigator monitoring and formal monitoring committee:
The Investigator monitors the study as noted above, with oversight by a DMC/SMC/DSMB. The protocol should contain a description of the committee, including its composition (numbers, area of expertise and names of the chair and its members, if known), frequency of meetings, schedule of reports, and specific responsibilities. Examples of study activities appropriate to this level of review:

- Multi-center clinical trials
- Gene transfer studies
- Blinded placebo-controlled clinical trials

OHSP Policy 506
Examples of Monitoring Operations

The following provides examples of appropriate types of monitoring and oversight for different types of studies. These are illustrative only. The ICs must develop and implement monitoring activities and oversight of those activities appropriate to the study, population, research environment, and the degree of risk involved.

Phase I: A typical phase I trial of a new drug or agent frequently involves relatively high risk to a small number of participants. The investigator and occasionally others may have the only relevant knowledge regarding the treatment because these are the first human uses. An IC may require the study investigator to perform continuous monitoring of participant safety with frequent reporting to IC staff with oversight responsibility.

Phase II: A typical phase II trial follows phase I studies and there is more information regarding risks, benefits and monitoring procedures. However, more participants are involved and the toxicity and outcomes are confounded by disease process. An IC may require monitoring similar to that of a phase I trial or supplement that level of monitoring with individuals with expertise relevant to the study who might assist in interpreting the data to ensure patient safety.

Phase III: A phase III trial frequently compares a new treatment to a standard treatment or to no treatment, and treatment allocation may be randomly assigned and the data masked. These studies usually involve a large number of participants followed for longer periods of treatment exposure. While short-term risk is usually slight, one must consider the long term effects of a study agent or achievement of significant safety or efficacy differences between the control and study groups for a masked study. An IC may require a DSMB to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations to the IC concerning its continuation.

DSMP IMPLEMENTATION
Prior to Enrollment

• Review DSMP charge
• Review protocol
  – study population
  – intervention (safety concerns)
  – pre-specified reportable events
• Establish SOPs/administrative procedures
  – Membership & voting
  – Meeting – timing/frequency/venue
  – Reports – timing, content/format (data summaries, table shells, & graphical displays, aggregate data by treatment group)
  – Meeting format (open and closed sessions, if blinded study)
  – Minutes – recording, distribution (open only)
Oversight Responsibilities

• Oversight of DSM activities – NIH considers distinct from the monitoring itself
• Conduct or delegate ongoing monitoring of interventional trials
• Ensure timely and effective monitoring
• Ensure those responsible for monitoring have the appropriate expertise to carry out charge
• Ensure timely response to recommendations that emanate from DSMB monitoring activities
Ongoing DSM Activities

- Periodic meetings per DSMP
- Evaluate data quality/timeliness, recruitment, accrual, retention, risk vs. benefit, site performance, etc.
- Monitor for scientific/therapeutic developments that may have safety or ethical impact
- Use collective judgment (in addition to data and statistics)
- May meet on emergent basis if issues warrant
On the Front Line...Site PI

- AEs, protocol-defined reportable events
- Elicit from direct subject contact, reports
- Document/interpret/report as required
  - Sponsor
  - IRB
  - Subjects
- If in doubt, ASK

Cartoonist: Don Mayne (www.researchcartoons.com)
On the Radar...

• Timely reporting of data enables timely monitoring
  – Data must be reasonably up to date for a DSMB to make appropriate recommendations and avoid erroneous conclusions

• Report unanticipated problems to the IRB

• Be mindful of schedule
  – Anticipate meeting report for IRB submission
  – Expect the unexpected
Tips & Tricks

• Calendar Ticklers
• Checklist
  – Pre-Review/Mtg
  – Review/Mtg
  – Post-Review/Mtg
  – Ongoing Events (compliance, unanticipated problems, SAE, early termination event, etc)
• Don’t be shy…ASK!
In Summary...

- Understanding purpose of a DSMP, function of DSMB and partnership of all responsible parties is key to ensuring safety of participants and integrity of the data.
- Plan ahead and ensure appropriate oversight and implementation of responsibilities through the study life cycle to ensure adherence to DSMP and optimal safety monitoring.
Questions?
HO! HO! HO! ... AND HAVE YOU BEEN A GOOD LITTLE PRINCIPAL INVESTIGATOR THIS YEAR?

ANNUAL REVIEW
Or more frequent as needed

Cartoonist: Don Mayne (www.researchcartoons.com)
References


ICH Guidance for Clinical Trial Sponsors (Establishment and Operation of Clinical Trial Data Monitoring Committees) E6 (5.5); E9


