Data and Safety Monitoring

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Objectives

- Identify potential data and safety issues related to your proposed study
- List at least 3 important duties of a Data and Safety Monitor (DSM)
- Describe the function and operation of a Data and Safety Monitoring Board (DSMB)

Why do you need a DSM plan?

- To establish procedures for monitoring and protecting the safety of participants
- To outline a system for ensuring the integrity and validity of the research data
- To satisfy the requirements of sponsors and institutional review boards

What studies require a DSM plan?

Multicenter randomized trial of a new surgical procedure?

Single-center trial of a low-risk diet and exercise program?

Phase 1 pilot of an established drug for a new indication?

Observational cohort study of older women with diabetes?

Approaches to data & safety monitoring

	Formal DSM plan	Multi-person DSMB	Interim monitoring	Stopping for harm	Stopping for efficacy
Multicenter trial of new surgical procedure	✓	✓	✓	✓	✓
Single-center trial of diet and exercise program	✓	?	✓	✓	?
Pilot trial of established drug for new indication	✓				
Observational study of women with diabetes					

Common components of a DSM plan

1) Summary of the potential risks of study procedures
2) Outline of procedures to protect data integrity and security
3) Plan for monitoring adverse events or alarm findings
4) Designation of person(s) responsible for overseeing safety
5) Plan for interim monitoring and/or stopping guidelines

1) Potential risks of study procedures

- What are the possible side effects of study treatments?
- What risks or discomforts may result from study tests?
- Any discomfort from questionnaires or interviews?
- Any special risks associated with loss of privacy?

Possible steps to minimize risks

- Exclusion of populations at greatest risk
- Special training or qualifications of staff
- Surveillance systems to detect early harm
- Special procedures to protect privacy

Examples of potential risks

(for trial of high-dose vaginal estrogen ring in menopausal women)

Procedures	Risks/discomforts
Treatment with high-dose vaginal estrogen ring	→ Vaginal discharge or irritation, possible ↑ risk of endometrial cancer
Endometrial biopsy to assess for endometrial hyperplasia	→ Bleeding, pelvic infection, puncture of uterine wall
Questionnaires about sexual activity and function	→ Discomfort or embarrassment from answering sensitive questions
Questionnaires about history of sexually transmitted disease	→ Risks to reputation in setting of loss of confidentiality

Examples of steps to minimize risks

(for trial of high-dose vaginal estrogen ring in menopausal women)

Procedures	Risks/discomforts
Possible ↑ risk of endometrial cancer	→ Exclusion of women with history of endometrial cancer
Risk of puncture during endometrial biopsy	→ Certification of healthcare personnel performing biopsy
Discomfort or embarrassment from questionnaires	→ Use of sealed envelopes for return of sensitive questionnaires
Risks to reputation in setting of loss of confidentiality	→ Use of study ID numbers on dataforms, database security protections

2) Protection of data integrity and security

- What systems will be used to enter and manage participant data?
- How will you maintain participant confidentiality during data collection?
- How will you protect the security of the study database?

Protecting data security and confidentiality

(for clinical trial of high-dose vaginal estrogen ring)

- Storage of data on password-protected servers
- Use of data encryption software on computer tablets
- Use of study ID numbers or acrostics on data forms
- Plan for protecting, then destroying identifiers

Protecting data accuracy and integrity

- Double data-entry procedures
- Verification of data by outside party
- Software with automatic checks for outliers
- Posting of queries for missing data values

3) Plan for monitoring adverse events

- **HOW** will you define adverse events (AEs)?
- **WHEN** or how often will AEs be assessed?
- **WHAT** procedures will be used to detect AEs?
- **WHO** will be notified about AEs as they occur?

Common AE definitions

- **Adverse event (AE)** = any negative change in health occurring while participants are on treatment, regardless of apparent relationship to treatment

- **Serious adverse event (SAE)** = death, disability, or unexpected hospitalization or prolongation of hospitalization while on treatment

Common AE assessment procedures

- Systematic assessment for AEs at follow-up visits
- Standardized questions and forms to record AEs
- Assessment of timing/duration and severity of AEs
- Possible attribution of AEs to study treatments
- Reporting of AEs/SAEs to IRBs, DSMs, sponsors

Follow-up of alarm findings

(Ex: cohort study of older women with diabetes involving serial ECG measurements)

- How will you notify participants' usual healthcare providers about concerning ECG findings?
- How will you preserve the distinction between research findings and clinical care?

4) Designation of a safety monitor

- Is independent data and safety monitoring needed for this study?
- If independent monitoring is needed, is one DSM or a multi-person DSMB indicated?
- What qualifications or experience should the DSM or DSMB members have?

Functions of a DSM or DSMB

1) Evaluate adequacy and timeliness of recruitment and adherence to protocol

2) Monitor participant safety including trends in AEs and SAEs

3) Consider external factors when they may have an impact on safety

Functions of a DSM or DSMB (cont.)

4) Evaluate the quality and integrity of data management and security

5) Make recommendations on continuation, termination, or other modifications

Who should serve as a DSM?

(Ex: clinical trial of high-dose vaginal estrogen ring)

- Clinician experienced in menopausal or genitourinary health?
- PhD-trained statistician or other statistical expert?
- Experts in clinical trial design or research bioethics?
- Representatives of sponsors, other stakeholders, laypersons?

5) Interim monitoring and stopping rules

- When should the DSM or DSMB review the data?
- What issues should be reviewed at each time point?
- What procedures will be followed during review?
- How should decisions about stopping early be made?

When and what issues to monitor?

Early issues:

- Problems with trial design
- Success of recruitment
- Success of adherence
- Loss to follow-up or drop-out
- Data quality and timeliness
- Information from other studies

Later issues:

- Early evidence of clear benefit
- Early evidence of clear harm
- Lack of conditional power to meet goals

Developing a monitoring schedule

- **Prior to start of recruitment:** review the study protocol and DSM plan
- **Soon after start of recruitment:** review rates of recruitment, adherence, follow-up
- **Periodically throughout trial:** re-review recruitment, adherence, follow-up, and assess efficacy and harm

Procedures for DSM or DSMB review

- Circulation of data tables prior to DSM review
- “Closed” vs “open” meetings to preserve blinding
- “Voting” vs “non-voting” DSMB members
- Summary and recommendations made by DSM Chair

Why stop a study early?

- Harm clearly demonstrated
- Benefit clearly demonstrated
- Not possible to demonstrate benefit
- Question answered by another study

Stopping for harm versus benefit

(Ex: clinical trial of high-dose vaginal estrogen ring)

- Scenario 1: Early evidence of increased risk of endometrial hyperplasia
- Scenario 2: Early evidence of clear benefit for reduction in genitourinary symptoms

Statistical issues in interim monitoring

- Statistical corrections to minimize chance findings from repeated interim monitoring
- Studies with multiple outcomes may require global indices to capture overall benefit vs harm
- Calculation of conditional power to provide compelling evidence of benefit or harm

Conclusions

- Data and safety monitoring is an important part of clinical research design
- Monitoring strategies depend on the type of study and associated risks
- Interim monitoring should address data quality, evidence of harm, and evidence of benefit