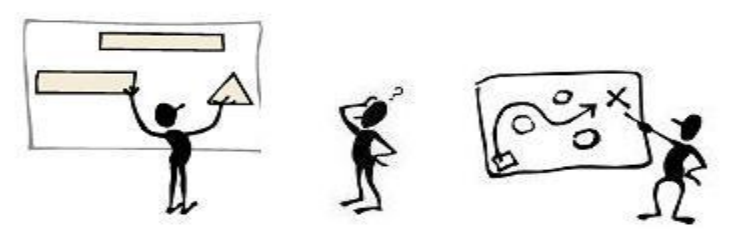
Planning for Data and Safety Monitoring:

Developing Your Study-specific DSMP



OCR/GCRC Clinical Research Seminar

November 15th, 2006

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Today's Topic

- Data Safety Monitoring Plans (DSMPs)
  - DHHS OHRP and FDA CFR
    - 45CFR.111 (a) (6) and 21 CFR 56.111 (a) (6)
    - "The IRB must make a determination that, where appropriate, the research plan makes adequate provision for monitoring data collected to ensure the safety of subjects:
  - INSPIR Section H

Today's Topic

- Regulatory history related to DSMPs
- What is a DSMP
- How do I put a plan together that is suitable for MY study?

Some Recent Regulatory History

- **June 1979**
  - Every clinical trial should have a provision for data and safety monitoring
- **June 1998**
  - All clinical trials require monitoring
    - Commensurate with risks, size and complexity
    - Focus is safety and validity/integrity of the data
    - Each IC in NIH should have a system for overseeing monitoring
- **June 1999**
  - How to report AEs in multi-center trials
- **June 2000**
  - Recommendations for monitoring for Phase 1 and 2 trials
- **May 2001**
  - NCRR directed 78 GCRCs to develop RSA position
  - Assist with developing a DSMP
  - DSMP templates – ensuring required elements are in the plan

What is a DSMP?

- A plan and process, individualized to the study, that is developed in regards to the study purpose and design and prospectively defines the methods to be used by the Sponsor, PI and study team to oversee safety of study participants by on-going evaluation of study data.

- Purpose: ensure the safety of the participants and the integrity and validity of the data

DSMPs:
One Size Does Not Fit All…

Content of a DSMP

1) Assignment of the level of risk in the particular study.

2) Who is monitoring… what is being monitored… and at what frequency.
   - Description of what each individual or group will monitor
   - Indication of the frequency of monitoring for each of the individuals and groups listed
   - Description of stopping points, interim analysis (if applicable) and unblinding plan

3) AE Reporting
   - AE Definitions and AE grading and attribution scales
   - Description of AE reporting mechanism: what gets reported, to whom, and in what timeframe

Assignment of Risk Level

- Risk in clinical research: “probability of harm occurring as a result of participation in a research study.” *(IRB Guidebook)*

Assignment of Risk

- Risk related to research: combination of factors:
  - **Known side effects of intervention and procedures (and how much is not known… i.e. phase of study)**
  - **The disease or condition and the main outcomes**
  - Study design (logistical considerations)
  - Risk-to-benefit ratio
  - Potential for invasion of privacy/breech of confidentiality
  - Potential for psychological impact of the study
  - Study population
  - Conflicts of interest

Definitions of Risk

- Only “minimal risk” is specifically defined by the regulations (45 CFR 46.102 i) :

- “Probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Assignment of Risk:
Greater than Minimal Risk

- Definitions provide a framework from which decisions about the appropriateness of the level of monitoring can be made.

- Meant to serve as a *general guide.*
  .
- *Differ* from IRB categories 1 through 4 (Section E1 of INSPIR)

Assignment of Risk:
Categories Greater than Minimal Risk

Description/Example	Monitoring guidance
LOW: Minor increase over minimal risk. Increased probability of a low-severity event that is reversible (i.e. muscle/joint soreness).	PI and staff; team meetings to discuss AEs; possibility of independent reviewer if a COI.
MODERATE: Increased potential for AEs, but likelihood of serious harm rare. Low risk interventions in potentially vulnerable populations.	PI monitors on on-going basis with staff; indep. safety monitor or DMC may be utilized; DSMB in large multi-site studies.
HIGH: Potential for high incidence of AEs. Increased probability of serious and prolonged or permanent problems. Uncertainty about the nature or likelihood of adverse events.	Frequent monitoring by PI and staff; often necessitates independent monitor or DSMB.

Level of Monitoring . . .
Commensurate with Risk

Minimal risk, single site, low # ptps

PI monitoring at regular intervals…

High risk, multiple-sites, high # ptps

Multiple staff at local site, outside monitoring, DSMB, etc.

On-going Monitoring: Who, What, How?

- List of all individuals and groups who are monitoring.
- What is being monitored?
- How frequently is the monitoring performed?

On-going Monitoring: Who, What, How?

- Always PI – *at least* the PI

May also include:

- Members of the local study team
- Independent monitor (i.e. for PI/sponsor)
- Individuals at Sponsor level
  - Safety Officer
  - Medical Monitor
  - Outside monitor (from CRO or sponsor)
- Steering Committee or other sponsor group
- Outside independent monitoring group
  - DSMB

On-going Monitoring: Who, What, How?

- Data to monitor
  - Individual AEs
  - Progress of study, recruitment, accrual, retention, compliance, consents
  - Quality of data
    - CRFs, data entry, etc.
  - Security of data
  - Assessment of timeliness of data transfer
  - PE, lab data, non-lab diagnostic
  - And more…

On-going Monitoring: Who, What, How?

Monitoring focus should be:

- Trends for an individual participant which may show that participation in the trial has become too risky.
- Stopping rules (safety and efficacy) and Interim Analysis (plans, if applicable; specified in protocol)
- Developments which may change the risk-to-benefit ratio in response to which the study (as a whole) must be:
  - Changed?
  - Suspended?
  - Terminated?

AE Reporting

- Institutional policies
  - BUMC AE Reporting
- Regulations under which your study is conducted
  - HHS (45 CFR 46.103), FDA (drugs biologics: 21 CFR 312, 314.80; 600.80; devices: 21 CFR 812.150; unanticipated problems: 21 CFR 56.108), ICH GCP (3.38, 4.11, 5.17)
- Sponsor requirements
  - Each NIH IC will have its own specific policies
- Funding agency requirements (i.e. if different from “sponsor”)
- Requirements of the DSMB and/or Steering committee

AE Reporting

- Prospectively define:
  - AE definitions (serious and non-serious)
  - Severity (grades) ex:
    - World Health Organization Toxicity Criteria
    - Cancer Therapy Evaluation Program (CTEP) Common Toxicity Criteria (CTC)
  - Attribution
  - Reporting process (what, to whom, and in what timeframe)

AE Reporting

Category	Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4
Cardiac	HTN	None	Asymp., transient inc. by > 20 mm Hg (D) or to > 150 / 100 if prev. WNL. No tx required.	recurrent or persistent inc. by > than 20 mm HG (D) or to > 150 / 100 if prev. WNL. No tx req.	Req. tx	Hyper-tensive crisis
GI	Vomiting	None	1 episode in 24 hrs	2-5 in 24 hrs	6-10 in 24 hrs	>10 in 24 hrs; req. parenteral support

WHO Toxicity Criteria

AE Reporting

Attribution scale example:

- **Definite**: AE is clearly related to intervention
- **Probable**: AE is likely related to intervention
- **Possible**: AE is possibly related to intervention
- **Unlikely**: AE is doubtfully related to intervention
- **Unrelated**: AE is clearly not related to intervention

AE Reporting

Timeframe

Example: new drug under IND; serious, unexpected AE

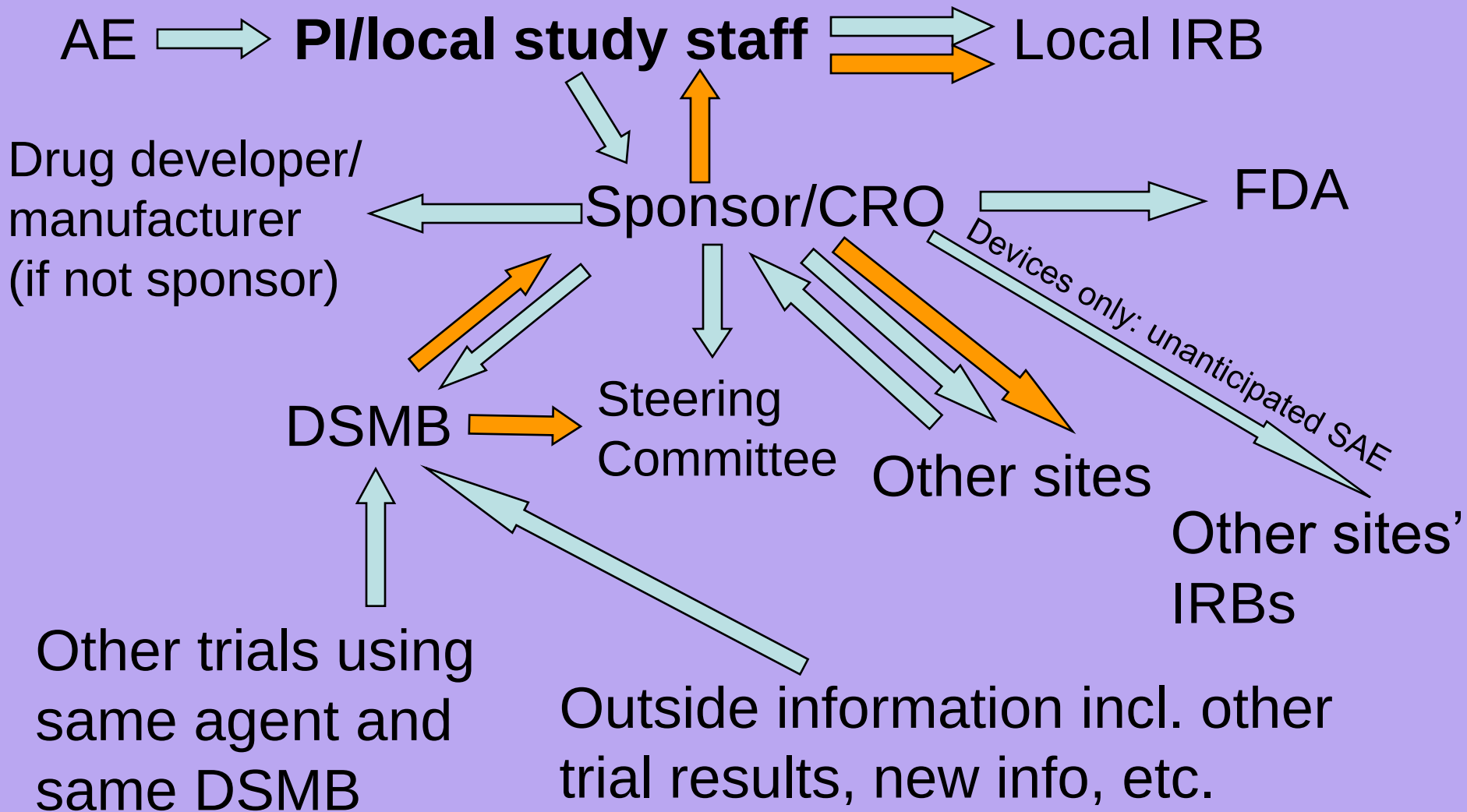
PI report to BU IRB by ph/fax w/in 24 hours and in writing w/in 2 business days for gr 4-5 and 10 days gr 3

Sponsor reports to FDA by ph/fax asap and in written safety report w/in 7 calendar days if life-threatening or death and w/in 15 calendar days if non-life-threatening.

Sponsor reports to other study sites via safety report within 15 calendar days.

AE Reporting

Example Scenario: Multi-center trial of new drug (under IND)



Conclusions

- The parts of a DSMP are: Assignment of the level of risk in the particular study; who, what, how the monitoring happens; and the AE reporting mechanism, including grading and attribution and what, to whom and in what timeframe do events get reported.

- Bottom line: planning for research participant safety and the success of your study.

Thank you!