IRBMED Seminar Series

Phase I Case Study
Institutional Evaluation and Regulatory Reporting
IRB Determinations
(from Mock IRB)

• Serious Adverse Event
• (Possible) Serious Noncompliance
• Unanticipated problem involving risks to subjects or others
Outcomes: Serious Adverse Event

A Serious Adverse Event (SAE) is defined by FDA and NCI as any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes:

1) Death
2) Life-threatening adverse drug experience
3) Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)
4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Congenital anomaly/birth defect
6) Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Outcome: Serious Noncompliance

Serious Noncompliance: Noncompliance that materially increases risks or causes substantive harm to research participants or materially compromises the rights or welfare of participants, including consideration of the following:

- Harm to participants;
- Exposure of participants to a significant risk of substantive harm;
- Compromised privacy and confidentiality of participants;
- Willful or knowing misconduct on the part of the investigator;
- A violation of ethical principles; or
- Damage caused to the scientific integrity of the data collected.
Outcome: Unanticipated Problem

- Unanticipated Problems Involving Risks to Subjects or Others (UaP)
  - It is “unexpected” in either
    - Nature
    - Severity
    - Frequency
  - It is “related” to the research; there is a reasonable possibility that the event may have been caused by the procedures involved in the research;
  - It suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
Institutional Actions

- Address subject safety
- Conduct fact-finding
- Corrective action
- Reporting obligations
Components of the HRPP

- Convened Board (full IRB)
- UMOR (*U-M Office of Research*)
- OoR (*Medical School - Office of Research*)
- ORCR (*Office of Research Compliance Review*)
- Regulatory Affairs
- General Counsel
- Office of Clinical Safety
- Public Relations

- Critical response team developed with above representatives
Examination of the Incident

Critical / Time-sensitive
• Suspension of the research
• Assess existing circumstances
• Medical treatment of impacted individuals
• Determine other subjects at risk
• Early notifications to external agencies

Fact-finding related to the incident
• Critical response team
  • Contributing circumstances still exist
  • Begin more detailed assessments
• IRB
• University offices
• Ad hoc faculty committee
• Sponsor / CRO
Examination of the Circumstances

• How did the event unfold?
• Was the protocol followed?
  ◦ Possibility of an error
  ◦ Was there an intentional protocol deviation
• Did the protocol design address all subject safety issues?
• Did the protocol have appropriate safety checks built in?
Review of Complaints or Concerns About Human Subjects Research

**DEFINITIONS:**
- IO: Institutional Official
- DIO: Deputy Institutional Official
- PI: Principal Investigator
- UMOR: University of Michigan Office of Research
- OHRCR: Office of Human Subjects Compliance Review
- EO: Executive Official
- CDM: IRB Chair and Director

*Complaints received from OHRP regarding U-M research are sent directly to the IO. UMOR will notify the DIO, PI, IRB Chair, IRB staff and others as appropriate. Complaints involving the IRB itself will be referred on a case by case basis.*

** Chair may ask for an administrative hold, which is not considered a suspension.**
Elements of Evaluation

IRB

The IRB determinations of the event:
- Serious Adverse Event
- Unanticipated Problem
- Serious and/or continuing Non-Compliance

Suspension of the Study (others also have ability to suspend research)

Assure all institutional HRPP components are aware of circumstances
Elements of Evaluation

**UMOR**

- Vice President for Research = Institutional Official for HRPP
  - Responsible party under the FWA

- Imposes any institutional sanctions or remediation requirements

- Makes external reports

- Receives internal reports as to progress of ongoing corrective actions
Elements of Evaluation

*OoR*

Works closely with UMOR and IRBMED to assure appropriate and timely response to the circumstances

May participate in assuring that ongoing corrective actions are met
Elements of Evaluation

**ORCR – Office of Research Compliance Review**

Conducts an independent audit of the research study
- Provide details of the event
- Interview individuals involved in the event

Provides ongoing monitoring of the study (if the suspension is lifted)

Audits/Monitors other studies under the oversight of the PI
Elements of Evaluation

Regulatory Affairs

Participates in the fact-finding and resolution of the incident

Close partner with UMOR and the IRBMED in evaluation, response, and any necessary ongoing oversight
Elements of Evaluation

Office of Clinical Safety

• Close partner with other offices to evaluate the clinical safety issues involved and indicated corrective actions
Elements of Evaluation

Public Relations

Provides accurate and timely information to the media and the general public

- External media sources
- U-M sources
Reporting Obligations

Federalwide Assurance of Compliance (FWA)
Appropriate institutional officials
Head of any federal department or agency conducting or supporting the research
  NIH
  Department of Defense
  Etc.
Applicable regulatory bodies
  OHRP (Office for Human Research Protections)
  FDA (for research subject to FDA oversight)
Regulatory Reporting

Written reports
- Detail of the incident
- Name of UM PI
- Any applicable federal funding
- Participant outcomes
- Root cause analysis
- Corrective actions
- Subject follow-up and notification as indicated

Agency response (Pat Ward will discuss further)
- Request additional information
- Site visit to U-M
- Institutional sanctions
- Individual (PI/study team) sanctions
Questions ?