

Monitoring, Reporting, and Subject Safety

DUHS IRB Symposium

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Vice-Chair, IRB



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Vice-Chair, IRB

- Dr. Kessler is currently the Chair of IRB 5 and the Vice-Chair of IRB 2. He has been a member of the Duke IRB since 1990.
- He has a special interest in medication safety and has chaired the United States Pharmacopoeia's Advisory Panel on Medication Errors and he has served on the National Coordinating Council for Medication Error Reporting and Prevention.
- Dr. Kessler completed a Fellowship in Postmarketing Surveillance at the University of Cape Town, South Africa. He received his Pharmacy degree from West Virginia University and his Doctorate degree from Duquesne University. He is Board Certified in Pharmacotherapy.



Learning Objectives

- Identify when a research protocol is required to have data and safety monitoring plans.
- Contrast minimal risk research and research in which the risks have been minimized
- List the investigator's reporting requirements to the IRB, FDA, sponsor and others
- Describe the characteristics of a viable corrective action/quality improvement plan, following an unanticipated problem (UPIRTSO)



Ethics and Regulations

- Ethical Principles
 - Beneficence
 - Non-maleficence
- OHRP and FDA regulations – “When/where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects”.
 - 45 CFR 46.111(a)(6)
 - 21 CFR 56.111(a)(6)



When is it appropriate to have monitoring plans?

- All research that is greater than minimal risk

Examples include:

- All prospective device studies (except some NSR devices)
- All prospective drug and biologic studies
- All prospective interventional studies
 - Surgery
 - Invasive monitoring
 - Certain types of behavioral research
 - Other



Distinctions of Risk

- Minimal risk research is a category of research defined by the FDA and OHRP
 - Research risks are no greater than risks encountered in the course of normal daily living of a healthy individual
- Research, in which the risks have been minimized, adequately controls for the new risks of being in the study – an ethical requirement!



Monitoring Plan(s)

How much monitoring is needed and how often?

- Appropriate for the degree of complexity and risk

The intensity varies:

- Multi-site vs. single-site
- Investigator initiated vs. collaborative research
- Blinded vs. open label
- Degree of uncertainty and variability



Examples of Monitoring Plan Resources

- **The investigator**
(Appropriate for a single site open label trial.)
- **An uninvolved expert in the research topic**
(Appropriate for a single site blinded trial.)
- **The sponsor's medical monitor**
- **The sponsor's monitoring committee**
- **An independent data and safety monitoring board (DSMB).**



**One
regulation
...for 2 plans**

**Data and Safety
Monitoring Plans**



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Monitoring Plan(s)

- Data monitoring and safety monitoring are distinct activities
 - Data Monitoring Plans
 - Validity and integrity of the data
 - Progress toward the research objectives
 - Validation of initial assumptions (e.g., accrual rate, subject characteristics)
 - Compliance with protocol
 - Safety Monitoring Plans
 - Safety of subjects (individual and population at risk)
 - Compliance with reporting requirements for adverse events and unanticipated problems

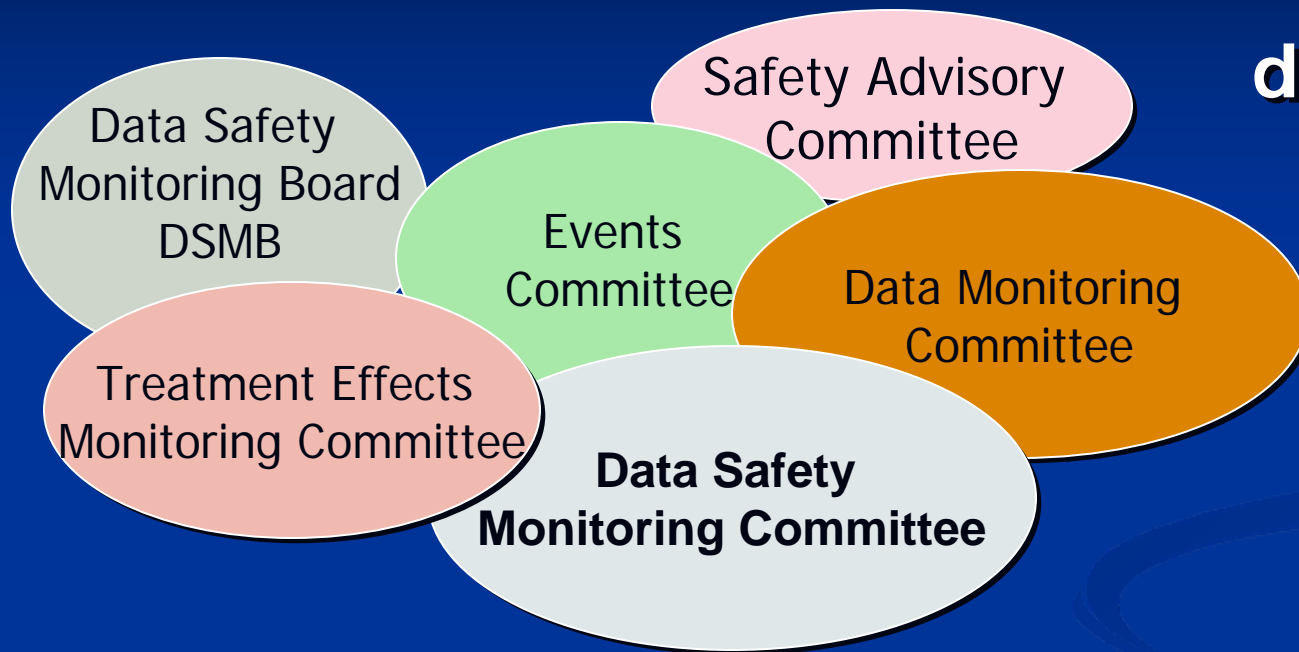


Plans vs. Boards/Committees

- All research studies involving more than minimal risk need a Data and Safety Monitoring Plan
- Data and Safety Monitoring Boards/Committees are not required except in selected instances
- FDA Final Guidance, approved March 2006, is at <http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>
- When a Board or Committee is chartered to review data, their INDEPENDENCE (i.e., no conflict of interest) is critical to appropriate analysis



Formal structures for data and safety monitoring



Does my study need a Data and Safety Monitoring Board (DSMB)?

- DSMBs are required in some instances:
 - NIH funded randomized studies
 - Emergency research studies in which the informed consent requirement has been waived (21CFR 50.24)
 - Requirement by the IRB



Does my study need a Data and Safety Monitoring Board (DSMB)?

- DSMBs are recommended when:
 - Large sample size
 - Multiple study sites
(more easily recognize a pattern of increased or unusual problems across multiple investigators)
 - Highly toxic therapies or dangerous procedures
 - High expected rates of morbidity or mortality
 - High chance of early termination of the study



Elements of a data monitoring plan

- Specify in the **Duke protocol summary** and in the **full protocol** (when applicable):
 - what data will be reviewed
 - who will review these data
 - how often review will be held



AEs, SAEs, and UPIRTSOs

How are these different?

and

What needs to be reported?



AEs are relatively rare events

All AEs



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AEs are relatively rare events and study related AE's are also uncommon....

A Venn diagram consisting of two concentric circles. The outer circle is larger and contains the text 'All AEs'. The inner circle is smaller and is centered within the outer circle, containing the text 'AEs-related to study'. Both circles have a red outline. The text is in a bold, orange-red font.

All AEs

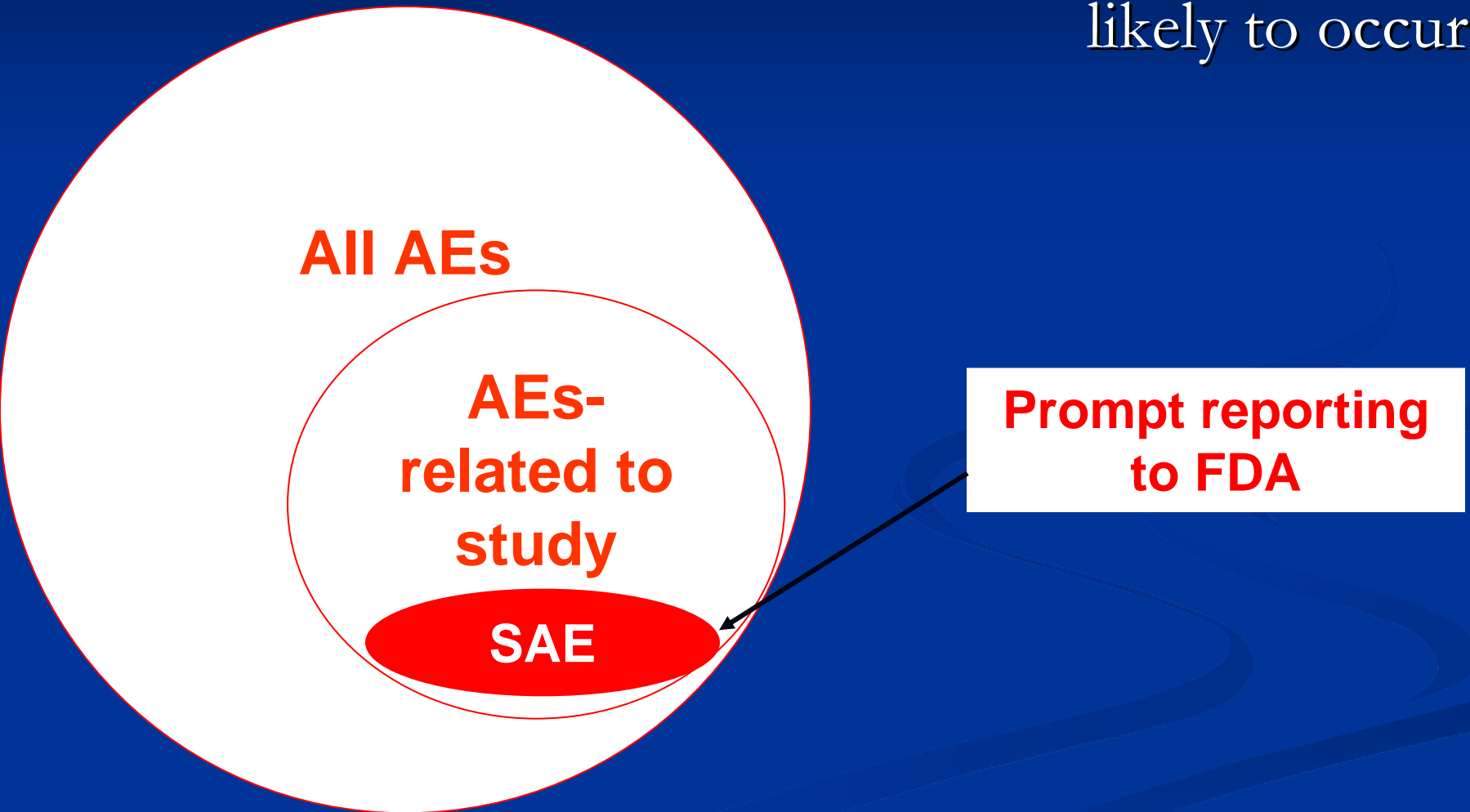
**AEs-
related to
study**

A red arrow originates from the right side of the 'Periodic AE reports' box and points towards the right edge of the inner circle in the Venn diagram.

**Periodic AE
reports**



AEs are relatively rare events and SAE's are even less likely to occur....



AEs are relatively rare events and SAE's are even less likely to occur....

All AEs

**AEs-
related to
study**

SAE/UaP

***UaP =
unanticipated
problems involve
risk to subjects
(UPIRTSO)**

**Prompt reporting
to FDA and IRB**



AEs are relatively rare events and SAE's are even less likely to occur....

All AEs

**AEs-
related to
study**

SAE/UaP

***UaP =
unanticipated
problems involve
risk but may not
result in an AE**

**Prompt reporting
to IRB and to
OHRP if DHHS
funded research**



Elements of an AE Reporting Policy

PI Responsibilities

As part of the larger Data and Safety Monitoring Plan, every AE must be reviewed by the Principal Investigator prior to reporting to the IRB. The Investigator must evaluate the AE in terms of:

- Causal relationship to the research
- Change in the risk-benefit relationship
- Adequacy of the current consent form
- Protocol changes
- Need to re-consent (or provide additional information to) enrolled subjects



Safety summary:

Reporting responsibilities*

■ Investigator

- AEs to sponsor 21CFR312.64(b)
- SAEs to sponsor 21CFR312.64(b)
- SAEs to IRB (“reportable” SAE’s as defined by local policy)
- UPIRTSOs to IRB 21CFR56.108(b)(1), (45 CFR 46.103(b)(5), 21CFR 312.53(c)(1)(vii), and 312.66

***Local IRB policies and special contractual agreements may also apply**



Safety summary:

Reporting responsibilities*

■ Sponsor

- AEs and SAE's to FDA 21CFR312.64(b)
- SAEs to IRB when risk is unreasonable and significant
21CFR312.56(d)
- UPIRTSOs to FDA, IRB and (Investigators if a device) 21CFR812.150(a)(1) and 812.46(b), 812.150(b)(1)
- SAEs with analyses to Investigator
21CFR312.55(b) and 312.32(c)(1)(ii)

***Local IRB policies and special contractual agreements may also apply**



Safety summary: Reporting responsibilities*

- **IRB** (more specifically...”institutional officials”)
 - UPIRTSOs to OHRP 45 CFR 46.103(a), (45 CFR 46.103(b)(5))

***Local IRB policies and special contractual agreements may also apply**



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Subject Safety and Systems of Care

- In the event of an unanticipated problem involving risk to subjects and others (UPIRTSO), the PI is required to report to the IRB:
 - 1. What actions were taken to address/correct/resolve the event?
 - 2. What actions are being implemented to minimize the likelihood of recurrence of the event in the future?



Subject Safety and Systems of Care

- In the event of an AE or UPIRTSO that is a **medication-related or patient care-related problem**, the PI should also report the event to the Duke Health System Safety Reporting System <https://srs.duhs.duke.edu>

(UPIRTSO Guidance Document Duke 2007

http://irb.duhs.duke.edu/wysiwyg/downloads/UPIRTSO_form_guidance.doc)



Corrective Action/Quality Improvement Plans

- Actions taken to minimize the likelihood of recurrence of the event in the future should be based on the **systems failures** that may have led to the problem.
- The IRB will review all proposed actions for their appropriateness and likelihood to reduce the risk in the system.
- Action plans, primarily based on education, counseling, discipline, posters, emails, and other temporal measures may be rejected by the IRB as insufficient to prevent future events.



Conclusions

- **Monitoring** of the data is an essential part of the research plan for subject safety
- **Reporting** AEs and UPIRTSOs is an essential part of the research plan for safety and compliance
- **Safety** is the result of good planning and good execution of the research plan

