VICE PRESIDENT FOR RESEARCH

UT HEALTH SCIENCE CENTER™

OFFICE OF CLINICAL RESEARCH

Conducting Clinical Research

November 13, 2008

7:30 a.m. – 5:00 p.m.

Sponsored by the Vice President for Research and Office of Clinical Research

Conducting Clinical Research

Program Objectives

The overall objective for this one-day training course is to provide Faculty Investigators, Research Nurses, Research Coordinators and Project Coordinators with a basic, “how-to-do it” approach to clinical trials, explaining how these procedures help to protect human subjects and provide valid data to answer the research question(s), while linking all of this FDA/DHHS and ICH Good Clinical Practice regulations and guidance. The individuals chosen to present each section of this training course are key personnel in the administration and/or the implementation of research at University of Texas Health Science Center at San Antonio (UT HSC), the South Texas Veterans Health Care System (STVHCS), or the University Hospital System (UHS).

While this course is designed to be accessible to new members of a research team, there is considerable new content in this course that will interest experienced research nurses and coordinators. Currently this course is scheduled to be repeated three times per year.

AGENDA
CONDUCTING CLINICAL RESEARCH
November 13, 2008

	No.	Topic	Presented by
8:00-8:10	1	Introduction/Pretest	Brian Herman, PhD Vice President for Research
8:10 - 8:30	2	Regulatory Background & Key Definitions	Kay Perry, JD Regulatory Affairs Analyst for Research Operations
8:30 - 9:05	3	Responsible Conduct of Research	Joseph Schmelz, PhD, RN, CIP Director, IRB
9:00 - 9:40		Investigator Responsibility	
9:40- 9:55	☺	**Morning Break (On Site)**	
9:55-10:55	5	Clinical Trial Project Management & Processes	Holly Nolan, MS Director, Office of Clinical Research Karen Aufdemorte, BA, HT (ASCP) Project Coordinator OCR Kay Perry, JD Regulatory Affairs Analyst for Research Operations
10:55-11:40	6	Industry Monitoring Audits & Compliance Reviews	Anna G. Taranova, Manager of Clinical Study Monitors Office Regulatory Affairs & Compliance
11:40-12:00	7	Scope of Practice	Peter Melby, MD STVHCS Assoc. Chief of Staff for Research
12:00-12:45	☺	**Lunch Break (Boxed Lunch Provided)**	
12:45 - 1:45	8	The Informed Consent Process	Robin Tragus, RN, MSN, Anne Leonard, MPH, RN, CCRC, FAHA, Karen Aufdemorte, BA, HT (ASCP), Erika Hess, BA, MS Lillian Sanchez, MSN, RN Eleanor Montalbo, Regulatory Affairs Coordinator
1:45 -2:15	9	Data Safety Monitoring Plan	Kimberly Summers, PharmD STVHCS Research and Development
2:15 - 2:35	10	Data Integrity	Dawn Lantero, PhD Research Subject Advocate
2:35 – 2:50	☺	**Afternoon Break (On Site)**	
2:50 - 3:35	11	Documentation: The Essential Regulatory Documents	Lillian Sanchez, MSN, RN Research Nurse III, OCR
3:35 - 4:15	12	Study Drug Accountability	Jennifer Hillman (UHS), PharmD Scott Soefje (CTRC), PharmD Virginia Doyal (VA) PharmD, BCPS
4:15 - 4:45	13	Adverse Events (UPIRSO)	Roy Estrada, PhD, PA-C, CIP Associate Director IRB
4:45 - 5:00	14	Post-Test Reviews/Evaluations	Holly Nolan, MS Director, Office of Clinical Research

Introduction

Brian Herman, PhD
Vice President for Research

Conducting Clinical Research

SPONSORED BY

Office of Clinical Research (OCR)

Office of the Vice President for Research

UT Health Science Center San Antonio

Continuing Education Credit

To receive continuing education credit, the participant must submit completed and signed – a statement of attendance **and a program evaluation at the end of the presentation**

- **For nurses CNE credits are awarded for 85% or more participation in this activity.** This continuing nursing education activity was approved by the Texas Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. This activity, CNE ID # O-AO-12676-02-08, meets **Type I** criteria for mandatory continuing education requirements toward relicensure as established by the Texas Board of Nursing.

- For physicians, the UT Health Science Center San Antonio School of Medicine* designates this educational activity for ***AMA PRA Category 1 Credits™***. **Physicians should only claim credit commensurate with the extent of their participation in the activity**.

*Accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

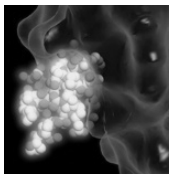
If you need proof of attendance for a certification you hold, make sure you sign in/out and request a Verification of *Attendance* from the OCR.

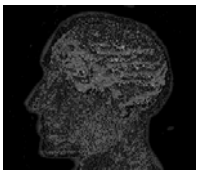
Faculty Financial Disclosure Information

- **Jenice Longfield, MD, reported she is a site visitor for AAHRPP research accreditation.**
- **Scott Soefje, Pharm D, disclosed that he is a consultant for Watson and Sanofi-Aventis Pharmaceuticals, a speaker for Merck and Eisai Pharmaceuticals, and holds stock in Amgen.**
- **Jennifer Hillman, Pharm D, reported that she holds stock in Pfizer Pharmaceutical and Johnson & Johnson.**
- **Anne Leonard, MPH, RN, CCRC, FAHA, disclosed she is a Stroke Consultant for the American Heart Association**
- **The other speakers and members of the planning committee have reported no conflicts of interest.**
- **Speakers will not discuss off label use of products.**

Introduction
by Brian Herman, PhD

Vice President for Research
Institutional Official (IO)





Navigating the HSC Website for Clinical Research Information

http://uthscsa.edu

http://research.uthscsa.edu/index.shtml **VPR**
http://research.uthscsa.edu/ocr/ **OCR**
http://research.uthscsa.edu/irb/index.shtml **IRB**

Regulatory Background
&
Key Definitions

Kay Perry, JD
Regulatory Analyst for Research Operations

Regulatory Background & Key Definitions

Kay M. Perry, J.D.
Regulatory Analyst for Research Operations
Office of Clinical Research
perryk3@uthscsa.edu
(210) 567-0452

Introduction

- Clinical trial:
  - a research study involving human volunteers to answer specific health questions
- Research:
  - a systematic investigation designed to develop or contribute to generalizable knowledge

Phases of Pharmacologic Trials

- Phase I
  - Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness
- Phase II
  - Controlled studies to evaluate the effectiveness of the drug and to determine the common short-term side effects and risks

Phases of Pharmacologic Trials

- Phase III
  - Expanded controlled and uncontrolled trials to gather additional information to evaluate the overall benefit-risk relationship of the drug
- Phase IV
  - Post-marketing study to assess additional information including the drug's risks, benefits, and optimal use

Device Trials

- Medical Device:
  - Class I
    - Minimal potential for harm; least regulated (general controls)
  - Class II
    - Special controls in place to ensure safety/effectiveness
  - Class III
    - Support human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury
    - Insufficient information assure safety and effectiveness solely through general or special controls.

Treatment Clinical Trials

- Evaluates a new treatment, or a new way of using a standard treatment

Federal Regulatory Agencies

Two offices, both part of the
Department of Health and Human Services (HHS):

The Food and Drug Administration (FDA)
&
The Office for Human Research Protection (OHRP)

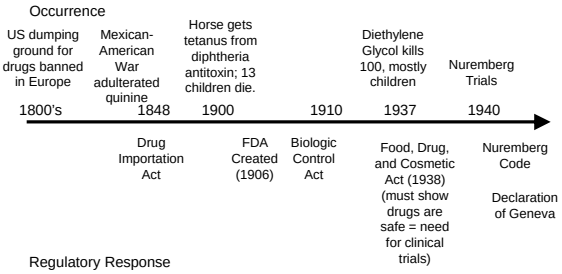
FDA

- Has oversight of the efficacy and safety of:
  - Food
  - Drugs
  - Medical devices
  - Biologics
  - Veterinary supplies
  - Cosmetics
  - Radiation-emitting electronic products
- Title 21, Code of Federal Regulations (CFR)

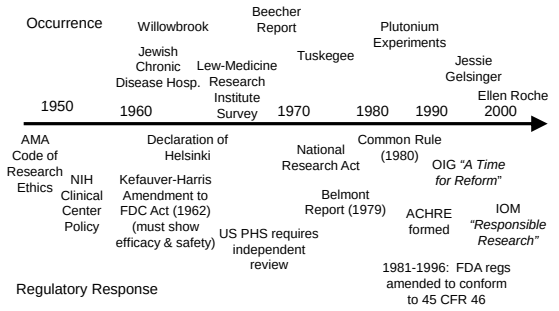
OHRP

- Ensures research conducted or supported by the HHS follows the requirements of 45 CFR Part 46
- Purpose: to protect the rights of research subjects

Evolution of Human Subjects Protection in Research Studies



Evolution of Human Subjects Protection in Research Studies



1966–1978: US Legal Response to the 1964 Helsinki Declaration

- **FDA Regulations:** specific requirements of informed consent defined [**21 CFR 130.37**, later incorporated in **45 CFR 46**]
- **OHRP/DHHS Regulations:** IRB procedures established, as well as special protections for vulnerable populations [**45 CFR 46**]

International Conference on Harmonisation

- 1996 – Good Clinical Practice Consolidated Guideline (E6)
  - Good clinical practice as an international standard that provides public assurance that trial subjects are protected. The U.S., the European Union, and Japan are all signatories.

Summary of Federal Regulation of Clinical Research – I

- [45 CFR 46] – Human Subjects Protection
  - (Subpart A is the Common Rule)
- [45 CFR 160 & 164] – HIPAA
- [45 CFR 94] – Conflict of Interest–Government Contracts

Summary of Federal Regulation of Clinical Research - II

- [21 CFR 11] – Electronic Records/Signatures
- [21 CFR 50] – Human Subjects Protection
- [21 CFR 54] – Financial Disclosure by Clinical Investigators
- [21 CFR 56] – IRBs
- [21 CFR 312] – IND Applications
- [21 CFR 314] – New Drug Applications
- [21 CFR 600] – Biological Products, General

Summary of Federal Regulation of Clinical Research - III

- [21 CFR 803] – Medical Device Reporting
- [21 CFR 812] – Investigational Device Exemption
- [21 CFR 814] – Pre-Market Approval for Medical Devices

Useful Websites & Key Definitions

- Federal Regulations
  http://research.uthscsa.edu/ocr/Summary.shtml
- NIH – Clinical Research Support
  http://www.clinicaltrials.gov
- Glossary of Clinical Trial Terms:
  http://clinicaltrials.gov/ct/info/glossary
  http://cancer.gov/dictionary
  http://www.aidsinfo.nih.gov/Glossary/GlossaryDefaultCenterPage.aspx

Questions?

Responsible Conduct of Research

Joseph Schmelz, PhD, RN
Director of IRB

Responsible Conduct of Research

Joseph Schmelz, PhD, RN, FAAN, CIP
Director, IRB
University of Texas
Health Science Center, San Antonio

HISTORICAL CONTEXT
Research Ethics

1949	Nuremberg Code
1964 (rev 1975)	World Medical Association Declaration of Helsinki
1972	Tuskegee Syphilis Trials
1974	Congress Enacted National Commission for Protection of Human Subjects of Research
1979	Belmont Report Published
1991	15 Federal agencies adopted Common Rule Office for Protection from Research Risk (OPRR) NIH
1995	National Bioethics Advisory Committee
1998-2001	OPRR Audits ⟶ Research Suspensions Office for Human Research Protection (OHRP) HHS

Belmont Report

- Identified three basic ethical principles
- "Belmont Principles"
  - Respect for Persons
  - Beneficence
  - Justice
- Each of the three has equal moral force

Respect for Persons

- Treat individuals as autonomous agents
- Not a means to an end
- Choose for themselves; provide extra protection to those w/ limited autonomy
- Obtain informed consent
- Respect for privacy of research subjects

Beneficence

- Minimize harms and maximize benefits
- Use best possible research design
- Make sure researchers are competent
- Deny research without a favorable risk-benefit analysis

Justice

- Distributive Justice
  - Burdens/Benefits
- Treat People Fairly
  - Select Subjects Equitably/Access
- Avoid Exploitation of Vulnerable Pop's
  - Example: Tuskegee

Responsible Conduct of Research

Federal Regulation

"The Common Rule" 45 CFR 46

FDA 21 CFR 50,56

HIPAA 45 CFR 160, 164

THE COMMON RULE

3 Basic Protections

- **Institutional Assurances**
- **Institutional Review Board**
- **Informed Consent**

Problems Identified - OPRR Audits

Inadequate Consent - Psych pts
Electrophysiology study - Pt refused x 2
Volunteer Harassment
Consents lacking, obtuse, misleading

- **IRB members - conflict of interest**
- **IRB members - coerced**
- **Subject file – database mismatch**
- **Late Continuing Reviews**
- **Failure or Late Report of Adverse Events**

OPRR Research Suspensions 1998 - 2001

West LA VA/UCLA	Univ. of Colorado
Duke	Univ. of Alabama
Univ. of NY/Mt Sinai	VA Commonwealth
Univ. of IL@Chicago	Univ. of Penn
Univ. of South Florida	Johns Hopkins

Adverse Patient Outcomes
Volunteer Death

Volunteer - OTC Metabolic Disorder (mild)

Univ of PA - Gene Rx Research

- Failure to inform of risk
- Failure to report previous AEs
- PI Conflict of Interest

Adverse Patient Outcomes
Volunteer Death

Volunteer - Healthy employee

Johns Hopkins - Hexamethonium

- Inadequate Literature Review
- Inadequate Risk in Consent
- Failure to Report AE of Previous Subject
- Failure to obtain IND from FDA

Increased Scrutiny

- Establishment of OHRP - Office for Human Research Protection
- Deans of Science ⟶ Resign or Worse
- New Requirements
  - IRB Program
  - IRB Chair
  - IRB Administrator
  - Principle Investigators and Research Staff

NEW INITIATIVES STRENGTHEN HUMAN RESEARCH SUBJECT PROTECTION

- Mandatory Education Requirement
  PI, IRB, Research Staff
- Enhance Informed Consent Process
- Audits, Monitoring, Oversight
- Clarify Conflict of Interest Regulations
- Research Accreditation Initiatives

SPECIAL TOPICS

Exempt, Expedited, Full IRB Review
Serum/Tissue Bank Research

Responsible Conduct of Research

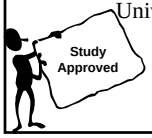
- **Institutional Commitment**
  - **Mandatory PI Training**
  - **Regular IRB Member Training**
  - **PI Instruction/Protocol Manual**
- **Mentors - Teach Importance of**
  - **Regulatory File**
  - **Case Report Forms**
  - **Procedures/SOPs**
  - **Research staff/training**
  - **Ethical Modeling**

Investigator Responsibility

Joseph Schmelz, PhD, RN
Director of IRB

Investigator Responsibilities

Joseph Schmelz, PhD, RN, FAAN, CIP
Director, IRB
University of Texas Health Science Center
At San Antonio



Principal Investigator's Relationship with Staff

A responsible PI will:

- Obtain team management skills
- Encourage questions from colleagues and staff
- Listen to the concerns of the research staff, as they may be the first to point out problems with the protocol and with compliance
- Build consensus with the research team
- Eliminate intimidation by those in supervisory positions
- Authority relationships are not limited to the PI and the staff, but can also include the authority of the sponsor over the PI, the authority of the PI over the subject, and the authority of the protocol over the PI.

CITI Course

Investigator-Subject Relationship

- The investigator must place the subject's rights, welfare, and safety above all other personal and scientific concerns.
- The relationship between researcher and subject is similar to a physician-patient relationship, but different in the following ways:
  - Informed consent is required for participation in research.
  - Withdrawal from a study is at the discretion of the subject.
  - Investigators should be sensitive to power relationships.
  - The investigator has a moral fiduciary relationship with the subject.

CITI Course

PI Responsibilities

- Initial Approval
- Continuing Review & Re-approval
- Amendment & Modifications
- Adverse Event/Unanticipated Problem
- Reports of Noncompliance
- Inactivation

Continuing Review

- Study approval no longer than 1 year
- IRB must review the protocol, any amendments, and
- a status report including:
  a) number of subjects accrued;
  b) description of adverse events, unanticipated problems, withdrawal of subjects, complaints,
  c) summary of relevant information;
  d) copy of current consent document(s)

Amendments & Modifications

- Changes in previously approved studies cannot be made without prior IRB review;
  - except when necessary to eliminate immediate hazards to a subject
- For example – changes in:
  - number subjects consented
  - design, methods or procedures
  - study staff, study sites/locations
  - consent procedures, consent document
  - recruitment advertisements, payments

Incidents, Experiences or Outcomes

Information of actual harm can be:

- an adverse event (encompassing both physical and psychological harms); or
- a problem or event not considered an adverse event** (encompassing social or economic harms)

Information indicating an increased risk of harm is:

- a problem or event not considered an adverse event** that place subjects or others at increased risk of harm than was previously known or recognized, but no harm occurred.

[** referred to as "non-AE incidents, experiences or outcomes"]

Unanticipated Problems / Adverse Events

any incident, experience or outcome that meets all of the following criteria:

(1) unexpected (in terms of nature, severity, or frequency);

(2) related or possibly related to participation in the research; and

(3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Putting it all together

- Consent requires "reasonably expected risks"
- Local safety monitoring requires a plan for assessing incidences, experiences and outcomes to determine whether unanticipated problems have occurred
- Promptly report UPIRSOs and take action to eliminate an immediate risk

Reporting Noncompliance

- Conducting research in a manner that disregards or violates federal regulations, failure to follow the IRB requirements & determinations, or institutional policies and procedures (in the case of VA research includes the requirements of the VA Handbook 1200.5)
- Handled by governing IRB
- Elevated to next higher management echelon
- Findings of serious or continuing noncompliance reported to:
  - HHS supported – OHRP
  - IND/IDE - FDA

Inactivation of IRB Approval

- When is it appropriate to inactivate IRB approval?
  - Enrollment of new subjects is permanently closed
  - Data, private information, and/or clinical specimens are no longer being collected for research purposes (including long term follow up)
  - Subjects are no longer being treated under the research protocol (includes no plan for future research treatment)
  - Research assessments or procedures are no longer being performed (includes no plan for future research procedures)
  - Federal research funding for this study is closed
  - If a multi-center study where UTHSCSA is the study operations center or the UTHSCSA investigator is the Lead Investigator, if the study closed at all participating sites
  - Data/specimen analysis has been completed locally, or if analysis continues locally and the data has been permanently de-identified

Investigator Responsibilities UTHSCSA Module - CITI

- protecting the rights and welfare of research participants and others associated with the study.
- ensuring that no portion of the research work that involves a human subject is started without prior written approval from the Institutional Review Board (IRB).
- maintaining written records of IRB reviews and decisions.
- obtaining the informed consent / authorization of subjects before the subject is involved in the research. using the currently approved (stamped by the IRB with an approval and expiration date) consent form (in studies where consent forms are required).
- maintaining all signed consent documents
- obtaining the appropriate HIPAA waiver prior to a record review or database search to identify potential subjects.
- recording consent for research in the patient's record (as appropriate) as defined by the institution's policy.

Investigator Responsibilities UTHSCSA Module – CITI (continued)

- reporting proposed changes in previously approved human subject research activities to the IRB, through the OIRB. The proposed changes will not be initiated without prior approval, except where necessary to eliminate apparent immediate hazards to the subjects.
- monitoring deadlines and submit a fully completed Progress Report to IRB prior to expiration of the study approval.
- ensuring the confidentiality and security of all information obtained from and about human subjects.
- submit a final report when the study is complete.
- prompt reporting to the IRB (and other applicable agencies) any unanticipated problems involving risks to subjects and others.
- following applicable Food and Drug Administration (FDA) regulations for all research involving drugs, biologics and medical devices.

Common Pitfalls

- Informed Consent Document - current version
- Consent Documentation
- Notes to file
- Privacy vs. confidentiality
- Current version of protocol
- Provision of tools, instruments, or data forms
- Provision of advertisements
- Signature sheets, documentation of training, compliance documents
- Omissions and corrections in documentation

Summary

- Follow the approved protocol
- Supervise the study staff to make sure they are following the protocol
- Follow the regulations and policies related to research and privacy
- Supervise staff compliance with policy
- Protect participants
- Verify IRB approval

Summary (continued)

- Keep participants informed and ensure they are willing to continue participation
- Regularly collect and assess information about safety or unexpected problems
- Assure study staff is qualified to perform delegated tasks (education, training, experience)
- Provide on-going communication with staff
- confirm the data is accurate
- Maintain organized records

Clinical Trial Project Management & Processes

Holly Nolan, MS
Karen Aufdemorte, BA, HT
Kay Perry, JD

OCR Training
Conducting Clinical Trials

Clinical Trial
Project Management & Processes

1

Topics

- **Management Concepts**
- **Operational Considerations**
- **Budgeting & Billing**

2

Management Concepts

Holly R. Nolan, MS, MT (ASCP)
Director, OCR
nolanh@uthscsa.edu
210-567-0481

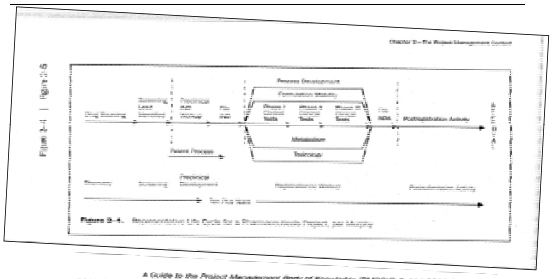
3

Main Points

- Project Management Environment
- Health Science Center Aspects of the Project Life Cycle
- Good Management Practices

4

New Drug Development Model
– The Project Management Context -



5

Clinical Research Stakeholders

See HOP 7.2.1

Organizational Components of the Human Research Protection Program (HRPP) Program Responsibility: Vice President for Research Institutional Official (IO)	
Conduct of Research	***Program Administration***
Principal Investigators Research Teams	**HRPP Steering Committee** Chair: AVP for Research Operations •VPR Offices oOffice of the Institutional Review Board (OIRB) oOffice of Clinical Research (OCR) oOffice of Sponsored Programs (OSP) oRisk Management & Safety •Office of Regulatory Affairs & Compliance •Senior Legal Officer •CTRC Investigational Drug Services •Representatives: oInstitute for Integration of Medicine & Science (IIMS) oIRB Chairs Representative oDeans of the Five UTHSCSA Schools oAffiliate Organizations - STVHCS , UHS, Christus Santa Rosa
Institutional Review Board	
Committees As Required (e.g. IBC, Radiation Safety, Radioactive Drug Research, Conflict of Interest)	
Department Chairs, Center or Institute Directors	

6

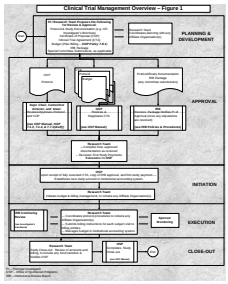
Phases – A Project Management Approach

- ❖Planning & Development
- ❖Clinical Trial Approval
- ❖Project Initiation
- ❖Protocol Execution
- ❖Project Close-Out

7

Overview of Clinical Study Project Cycle at the HSC

p. 2 of
OCR Guidance



8

Clinical Trial Approval

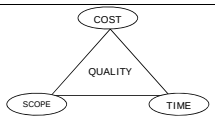
	OSP	IRB	Department Chair(s), Center/Institute Director(s), & Dean (as appropriate for the resources applied to the study)	Committee Review(s) (as applicable to the study)
Documents	▪ **Confidential Disclosure Agreement (CDA** ▪ **Clinical Trial Agreement (CTA)** ▪ Protocol & Budget ▪ COP	▪ **IRB Package** (with Protocol)	▪ **Certificate of Proposal (COP)** ▪ Protocol	▪ SACI Protocol Review Group ▪ Radiation Safety Committee ▪ Radioactive Drug Research Committee ▪ Institutional Biosafety Committee

The Principal Investigator:
- Participates in negotiating the final budget with sponsor and other members of the Research Team.
- Participates occasionally in the negotiation of the final CTA with the Sponsor and OSP.
- Resolves any IRB stipulations
- Coordinates CTA, COP, and IRB approval (receives IRB and CTA approval before initiating any study activities).
- *Registers study with Medicare (applicable to qualifying studies for which Medicare will be billed).*

9

Project Management Knowledge Areas

- ☐ Scope
- ☐ Time
- ☐ Cost
- ☐ Quality



- Project Integration
- Communications
- Human Resources
- Risk Management
- Procurement

10

Project Direction

- ☐ Technical
- ☐ Schedule
- ☐ Budget
- ☐ Procedural
- ☐ General Operations

11

Managing Conflicts

- ☐ Common Causes
  - Schedules
  - Priorities
  - Manpower
  - Technical
  - Procedures
  - Personality
  - Costs

Good planning serves to reduce issues.

- ☐ Create A Climate for Conflict Resolution
  - Pause – Think – React
  - Collect Information/Facts BEFORE Discussions
  - Recognize validity of varying viewpoints
  - Let Established Priorities Govern Decisions
- ☐ Use a Problem-Solving Approach
- ☐ Develop an Action Plan
- ☐ Execute the Action Plan
- ☐ Follow-up

12

Words to Manage by

"Stay in control of your study."

Follow the protocol and regulatory requirements

"Stay ahead of your processes."

Track and report progress

On time-On spec-On budget

Engage all members of the research team in planning the study and monitoring the progress.

13

References

- Draft FDA Guidance (distributed for comment purposes only, May 2007): Guidance for Industry Protecting Right, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators
- Project Management – A Systems Approach to planning, Scheduling, and Controlling, 8th Edition John Wiley & Sons, Inc., Harold Kerzner, PhD
- HSC HOP 7.2.1 HRPP Responsibilities http://www.uthscsa.edu/hop2000/7.2.1.pdf
- OCR Guidance for Management of UTHSCSA Clinical Trials: A Practical Guide Focusing on the Department Roles and Resource Management http://research.uthscsa.edu/ocr/OCR%20Guidance%20for%20Mgt%20of%20Clinical%20Trials.pdf

14

Operational Considerations

Karen Aufdemorte, BA, HT (ASCP)
Project Coordinator, OCR
aufdemortek@uthscsa.edu
210-567-1388

15

Basic Considerations

- ☐ **Protocol**
- ☐ **Budget and Resources**
- ☐ **Approvals**
- ☐ **Initiation**

16

Common Reactions

- **D**enial (this isn't *happening* to me!)
- **A**nger (why is this happening to *me*?)
- **B**argaining (I promise I'll be a better person *if*...)
- **D**epression (I don't *care* anymore)
- **A**cceptance (*I'm ready* for whatever comes)

17

Planning & Development

- ☐ Feasibility Assessment
  - ■ Affiliate Organizations
  - ■ Checklist Approach
- ☐ Budget Development
  - ■ Direct Costs
  - ■ Cost Per-Subject
- ☐ Planning & Coordinating the Billing

18

Contract versus Grant

Contract

- Agreement
- Deliverables
- Reporting Requirements
- Payment Schedules

Grant

- Type and Length
- Reporting Requirements
- Restrictions on Funds
- Carry Over Funds

19

Budget Items to Consider

- Amount of time spent with monitors
- Regulatory work
- Administrative support
- Pharm/Lab/Rads
- Equipment
- Records Storage
- Supplies
- Advertising
- Translation services
- Screening Failures
- Early Termination
- Travel
- Training
- Post-Study audits (FDA, sponsor, etc.)
- Personnel time (research team)

20

Investigator Involvement

- Staff Meetings
- Meeting with Sponsors
- Internal Assessment and QC
- Processes for Corrective Action
- Resource and Document Review

21

Commonly Delegated Tasks

- Recruitment
- Screening & Enrolling
- Sponsor/Monitor Communication
- Developing/Negotiating Budget
- Track CTA Approval
- Management of Subject Participation
- Administration of Investigational Article/Intervention
- IRB Communications
- Supervising Research Team
- Training
- Clinical Trial Billing
- Regulatory/Study Files
- AE/UPIRSO Reports
- Study Closure/Reporting

22

Delegation ≠ Abdication

P.I. is not short for Practically Invisible

Final Responsibility for Study Conduct is the ***Investigator***

http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0173-gdl0001.pdf

23

Study Execution

- Review/Develop Manual of Operations (MOO) or SOPs
- Hire/Allocate Staff
- Affiliate Interface
- Recruit Participants
- Maintain Study Compliance and IRB Approval
- Budget Oversight

24

Create an environment that is process-oriented

Standard Operating Procedures

- Operational Instruction
- Quality Foundation
  - Compliance
  - Consistency
    - On Schedule
    - Proper Interfaces
  - Audit resource
    - Quality Improvement
    - Trouble Shooting
  - Involve Staff in Content
  - Monitoring & Review
  - Make Readily Available
  - Train - Roles & Responsibilities
  - Revise SOPs Promptly

25


Document Your Processes

- Consider the Following:
  - Control Investigational Product
  - Your Consenting Processes
  - Manage Documents and Maintaining Essential Documents
  - Train the Research Team
  - Address Errors or Audit Findings & Prevent Recurrence (CAPA plans)
  - Standardize Routine Medical Care
  - Manage Personnel & Delineate Lines of Authority
  - Maintain the Facility & Equipment (e.g. calibrations, preventive maintenance schedules, cleanliness)
  - Manage the Clinical Trial Budget and Billing



The FRAMEWORK

GOOD PROCESS

- Clearly Defined Work and Milestones
- Established Processes to Ensure Compliance
- Qualified & Trained Research Team
  - Job specific requirements
  - Clear delegation of responsibility
- Properly Managed Study Documents
  - Routine Review
  - Fit the study requirements and processes
  - Proper Storage & Accessibility
- Regular Meetings
  - Study Initiation
  - Monitor Visits
  - Research Team Progress
- Communication - Research Team & Affiliates

GOOD HABITS

- Delegate Wisely
- Follow the Schedule
- Look Ahead & Monitor
- Optimize Meetings (#, time, objectives)
- Be Decisive
- Resolve Conflicts
- Learn to Say No
- Do the Tough Part First
- Overcome Procrastination (Start Now)
- Conduct Audits within the Research Team

27

Study Close Out

- ☐ Final Review of all Study Objectives
- ☐ Review Budget – All Billing and Payments Complete
- ☐ Prepare Final Sponsor and IRB Reports
- ☐ Notify OSP
- ☐ "Lessons Learned"

28

References

- OCR Guide for Management of Clinical Trials http://research.uthscsa.edu/ocr/
- The CRA's Guide to Monitoring Clinical Research, Karen E. Woodin, Ph.D. & John C. Schneider
- The CRC's Guide to Coordinating Clinical Research, Karen E. Woodin, Ph.D.
- The Thompson Guide to Good Clinical Practice

29

Insurance Aspects of Budgeting & Billing

Kay M. Perry, JD
Regulatory Analyst for Research Operations
PerryK3@uthscsa.edu
210-567-0481

30

Preparation Phase

- Make a grid: list all items/services and time intervals
- Determine what services are standard of care (SOC)
  - Would be done even if not on the study, at the same time interval

31

Budget Development Phase

What is billable to insurance?

What is not?

32

Medicare – IDE Device Trials Must Get Contractor Approval First

Category A Device
(innovative devices)

- Cannot bill for the device
- Routine services related to device may be billable

  If an "immediately life threatening disease or condition"

Category B Device
(safety & efficacy established)

- Device & routine services may be billable
- Factors:
  - medical necessity
  - frequency
  - acceptable medical standards
  - appropriate setting

33

Medicare – All Other Trials
(other than IDE Device Trials)

For all trials:

- SOC services/items
- Research-related injuries

34

Billing Medicare, continued

- For "qualifying trials" Medicare also pays for:
  - Administration of investigational drug
  - Detection and prevention of complications
- Referred to as "routine costs" (including SOC services)
- Which trials qualify?
- ✓ Trial funded by certain federal agencies ("deemed")
- ✓ Investigational item/service within a Medicare benefit category
- ✓ Study enrolls patients with diagnosed disease
- ✓ Study has therapeutic intent
  - Phase I trials do not qualify

35

Medicare does not pay for…

- The investigational item or service itself
  unless otherwise covered outside of the clinical trial, or covered under a National Coverage Determination (NCD) using Coverage with Evidence Development
- Items and services provided solely to satisfy data collection and analysis needs
  e.g., monthly CT scans for a condition usually requiring only a single scan
- Items and services customarily provided by the sponsor free of charge for any enrollee

36

Other Insurance Plans

- Commercial Insurance varies
  - many follow Medicare rules
  - managed care contract may address issue
- Medicaid
  - pays for SOC services

37

Always make it clear what the sponsor is paying for:

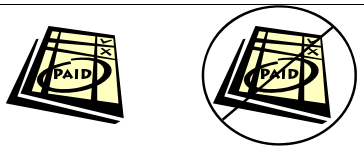
- Clinical services?
- Research personnel time?

Per Subject Fee
(By Visit)

Screen Failure Visit 1	–	$500.00
Screen Failure Visit 2	–	$316.25
Screen Failure Visit 3	–	$372.50
Screen Failure Visit 4	–	$300.00
Visit 1	-	$1,603.35
Visit 2	-	$398.48
Visit 3	-	$469.35
Visit 4	-	$1034.78
Visit 5	-	$579.60
Visit 6	-	$579.60
Visit 7	-	$603.23
Visit 8	-	$959.18
Visit 9	-	$839.48
Visit 10	-	$902.45
Visit 11	-	$1,374.98
Visit 12	-	$217.35
Telephone Contacts		$259.88
Total subject site budget		$9,821.70

38

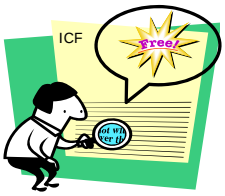
Do not double bill



EXCEPT for NIH Studies –bill for SOC services, but **MUST** credit research account

39

Do not bill for items or services promised for free in the ICF



= NO BILL

(to patient or insurer)

40

Negotiation Phase

- Just because sponsor says service is SOC, doesn't make it so
  - PI accountable for this decision, not the sponsor
- Indicate on your grid:
  - Services funded by sponsor
  - Billable services
  - Nonbillable services
- Have a billing plan based on final budget

41

During Study and Post-Study Analysis

- Did you receive all invoices from affiliates?
  - If not, they billed the wrong party, which must be corrected

42

What Research Personnel need to do:

- Establish roles and responsibilities
- Ensure there is no double billing
- If billing third party payers, ensure items are billable
- Look for opportunities to increase revenue
  - If sponsor will not pay for a billable item/service, ensure it gets billed
  - Detailed budget that includes all costs/items/services and strong negotiation skills

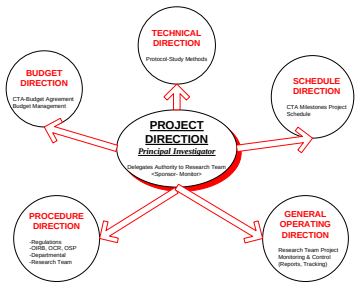
43

References

- HOP 7.8.1. (under revision)
- Drugs:
  - NCD for Routine Costs in Clinical Trials (310.1)
  - Medicare Claims Processing Manual Chapter 32, Section 69
- Devices:
  - Medicare Benefit Policy Manual Chapter 14, Section 20

44

In Summary – Clinical Trial Direction



45

Industry Monitoring Audits
&
Compliance Reviews

Anna G. Taranova
Manager of Clinical Study Monitors

OFFICE OF REGULATORY AFFAIRS & COMPLIANCE
UT HEALTH SCIENCE CENTER
SAN ANTONIO

Human Subject Research Compliance Reviews

Anna G. Taranova
Manager of Clinical Study Monitors

1

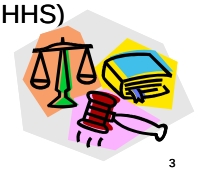
Agenda

- Types of Oversight Activities
- Compliance Review Process
- Common Findings from Compliance Reviews
- Practical Solutions

2

Regulations

- Good Clinical Practice (GCP) Guidelines
- FDA Regulations (Title 21 Parts 11, 50, 54, 56, 312, 812)
- The Common Rule (Title 45 Part 46)
- IRB Policies
- Sponsor Policies (Industry, HHS)
- AAHRPP
- HIPAA



3

Types of Oversight Activities

- FDA
- Sponsor
- Internal

4

FDA Audits

- Determine compliance with federal regulations & guidelines
- Verify validity & integrity of clinical data
- Assure participant rights, safety, & welfare protected
- Related to certain classes of investigational products (special interest in its current work plan)

5

FDA Audits

Types of Inspections

- Study focused
- Investigator focused
- Routine
- Directed/For Cause

6

FDA Audits

- Notification to PI
- Upon arrival FDA investigator issues Form FDA 482, “Notice of Inspection”
- Conducts audit
- Form FDA 483, “Notice of Inspectional Observations”
- “Establishment Inspection Report” (EIR)

7

FDA Audits

- Cooperate with FDA auditor
- Always notify IRB and Office of Regulatory Affairs & Compliance
- Assign a staff member to assist and document
- Do not answer a question if you are not sure of the answer

8

FDA Audits

Types of Reports

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)

9

External Sponsor Monitors

- Ensure compliance with protocol & GCPs
- Ensure data is high quality
- Validate integrity of data
- Ensure adequate facilities
- Ensure adequate staffing

10

External Sponsor Monitors

Types of Reviews

- Qualification
- Initiation
- Interim monitoring
- Close-out

11

Internal Compliance Reviews

- Office of Regulatory Affairs & Compliance
- Independent and objective function
- Reports to President's Office
- Reports sent to IRB for monitoring compliance

12

Objectives of Compliance Review

- Examine IRB approved studies for compliance
- Evaluate a study's progress, regulatory documentation maintenance, and overall conduct of study.
- Educate - an opportunity for investigators and research staff to ask questions

13

Why Me?

- Random reviews
- At the request of IRB or OCR
- For cause

14

Review Process

- Notification letter to PI with review tool
- IRB files reviewed
- Entrance meeting
- Study review
- PI summary
- Exit meeting with PI to discuss findings
- Final report to IRB
- PI response to findings (sent to IRB)

15

Review Focus

- Regulatory documents
- IRB submissions
- Informed consent
- Inclusion/exclusion criteria
- Research and participant files
- UPIRSO reporting
- Source documentation
- Investigational product (IP)
- Information security/confidentiality

16

Participant Selection for Review

- Less than 250
  - 10% or 10 (whichever is greater)
- Greater Than 250
  - At least 25 reviewed

17

Common Findings from Compliance Reviews

18

Informed Consent

- Need for translated consents
- Document consent process
- Latest version of consent not signed
- Executed consent does not have IRB stamp
- Incomplete and/or missing signatures
- Not obtained prior to research procedures
- Obtained by person not approved by IRB

19

Inclusion/Exclusion Criteria

- Enrolled, but criteria not met
- Criteria not adequately documented to verify eligibility
- Deviation not reported to IRB

20

Documentation

- Improper data correction
- No signature or date on forms
- Incomplete CRFs/not completed on time
- CRFs not supported or match source documents
- Electronic files are not on a secure server

21

Regulatory Documents

- SAEs not reported to IRB
- Continuing progress report errors
- Regulatory binder not well maintained
- Lapsed approval - untimely submissions
- Sponsor monitor issues not addressed in timely manner or not addressed at all
- Investigators & study staff not IRB approved

22

Investigational Product Accountability

- No master dispensing log
- No temperature log
- No documentation of instructions for IP use (taking & returning)
- Dispensed by a person not approved by IRB

23

PI Oversight of Study

- Adequate oversight in identifying deviations
- Study not conducted as approved
- Staff experience
- Non-responsive to sponsor reports

24

Consequences of Failing to Protect Human Participants

25

Consequences of Failing to Protect Human Participants

- Safety risk to participants
- Fines & penalties
- Publicity
- Jeopardizes reliability of data
- Decreased study recruitment
- Legal fees & settlement costs
- Loss of public trust in clinical research
- May shut down research for whole institution

26

Practical Solutions

- Check approval and expiration dates on each document before presenting to subject
- Make sure the IRB stamp is the most current
- Write a “Note to File” to document errors, deviations or omissions

27

Practical Solutions

- Maintain current documentation on file (protocol versions, CVs, progress reports)
- Drug dispensing/accountability log
- Staff responsibility log, signature log, required training records

28

Practical Solutions

- Stay involved, take control of your study
- Be inspection ready
- Conduct a self-audit
- Any questions – consult with Office of Clinical Research, Office of Regulatory Affairs & Compliance or IRB

29

New for 2009

- Standardization of studies – upcoming AAHRPP accreditation
- Revised tool for conducting reviews

30

Office of Regulatory Affairs & Compliance Resources

Anna Taranova, taranova@uthscsa.edu

Kathy James jameskd@uthscsa.edu

Gayle Knight, knight@uthscsa.edu

Office Number: (210) 567-2014

Anonymous Compliance Line 1-800-500-0333

31

Scope of Practice

Peter Melby, MD
STVHCS Assoc. Chief of Staff for Research

Scope of Practice for Research Personnel

Peter C. Melby, M.D.
Associate Chief of Staff for Research
South Texas Veterans Health Care System

Research Scope of Practice

What is it?

- A component of the Human Research Protection Program that is designed to ensure that research personnel are qualified to conduct the research
- Complementary to degree verification, credentialing, training, and competency assessment
- A tool to define and approve the duties and responsibilities of research personnel that are involved in human subjects research

Research Scope of Practice

A Valuable Tool

- Defines the duties and responsibilities of research personnel that are involved in human subjects research
- Ensures that the qualifications of the individual match the requested duties and responsibilities
- Clarifies the functions of individuals within the research team
- Documents the responsibility of the Principal Investigator in the oversight of research personnel
- Provides a means for institutional oversight of research personnel
- Helps to protect subjects enrolled in research protocols
- Helps to protect the integrity of research data

Research Scope of Practice

- Who is required to have a Research Scope of Practice
  - Research staff who interact directly with human subjects
  - Research staff who interact with Individually Identifiable human subject information
- Who is NOT required to have a Research Scope of Practice
  - Strictly administrative staff who have no contact with human subjects or their Individually Identifiable Information
  - Research personnel (e.g. statisticians) who only work with de-identified data
  - Clinical personnel who perform tests on research subjects as part of their routine clinical job

Research Scope of Practice

Criteria that govern the roles and responsibilities included in the Scope of Practice

- Education
- Experience
- Licensure
- Competency
- Applicable State and Federal Laws
  - Unlike clinical credentialing, very little guidance available
  - Not clear who can do what
- Institutional policy
  - Err on the side of human subject safety
  - Employ common sense
  - Consider public perception

Research Scope of Practice

Case Study

A research fellow, who has an M.D. degree from another country but is not licensed in the U.S., requests that his Research Scope of Practice include performing a 2 mm skin punch biopsy as part of a research protocol. He indicates that he has performed this procedure many times, and the Principal Investigator of the study attests that he is qualified to do it.

Is it acceptable to include this procedure as part of his Scope of Practice?

Research Scope of Practice

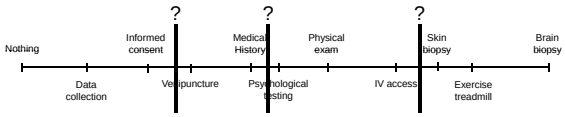
Case Study

A Principal Investigator, who studies stress and cognitive function, requests that the Research Scope of Practice for her research assistant include the obtaining of informed consent and the administration of neuropsychological testing. The PI has provided on-the-job training to the research assistant, who has a B.S. in Medical Technology.

Is this an acceptable part of her Scope of Practice?

Research Scope of Practice

What roles and responsibilities can research personnel have?



Where do you draw the line?

- For a licensed physician?
- For a licensed nurse?
- For a non-licensed research assistant?

Research Scope of Practice

Where do you draw the line?

Licensed personnel:

- Dictated by the regulations related to their license
- Responsibilities unique to research (not part of standard clinical training) require documented competency.
- If a research protocol requires a licensed physician to perform a procedure that is beyond his/her approved practice, then approval to perform the additional procedure must be obtained through the credentialing board

Unlicensed personnel (regardless of educational degree):

- Cannot perform any function that would constitute the practice of medicine
- Any procedure, that in the context of routine medical practice would require the consent of the patient, can only be performed by an appropriately licensed provider

Research Scope of Practice

South Texas Veterans Health Care System
University of Texas Health Science Center at San Antonio
Scope of Practice for Research Personnel

NAME	JOB TITLE
DEGREE	**LICENSURE**
❒ MD ❒ DO ❒ DDS ❒ NP/CNS ❒ PA ❒ RN ❒ BS ❒ MS ❒ PhD ❒ None ❒ Other:_____	❒ MD ❒ DO ❒ DDS ❒ NP/CNS ❒ PA ❒ RN ❒ LVN ❒ MT ❒ None ❒ Other:_____
PRINCIPAL INVESTIGATOR (PI)	**CREDENTIALING & PRIVILEGING STATUS**
	From:_____ To:_____

The Scope of Practice is specific to the duties and responsibilities of each research employee/staff as an agent of the listed Principal Investigator(s) for a term not to exceed two years. The employee is specifically authorized to conduct research involving human subjects with the responsibilities approved below in conjunction with approved research protocols. This document does not waive the responsibility to secure STVHCS clinical Credentialing & Privileging for any licensed independent provider under VHA Directive 1100.19 or other appropriate institutional privileging directives. The Scope of Practice is governed by the policies and procedures outlined in the STVHCS Hospital Policy

Research Scope of Practice

Routine Duties (may require competencies or credentials)	Licensed MD - DO, DDS	NP / CNS / PA	RN.	Other Licensed and Credentialed*	Non-Licensed*	Lab / Bench Staff	Competency ** Verification
Checks and records vital signs (requires competency verification by observation by PI)							
Performs physical examination (within limits of license)							
Evaluates acute health problems, including possible adverse events (within limits of license)							
Performs physical assessment (for RNs within limits of license; for non-licensed individual requires delineation of specific task(s) to be performed, and competency verification by observation by PI)							
Performs venipuncture to obtain specific specimens required by study protocol (requires formal training program through clinical laboratory, or a history of previous training and competency verification by observation by PI)							
Collects and/or processes human specimens per protocol, including blood, urine, sputum, buccal swabs, etc. (requires competency verification by observation by PI)							

Research Scope of Practice

NOTICE TO LICENSED PROFESSIONALS:
Individuals found to be working outside their privileges as granted by the STVHCS, UTHSCSA, or other UTHSCSA-affiliated institutions will be subject to disciplinary action and possible reporting to the National Practitioner Data Bank.

RESEARCH EMPLOYEE'S STATEMENT:
This Scope of Practice outlines general tasks I am permitted to undertake in conjunction with an approved protocol. I understand that all research must be approved by the UTHSCSA IRB, and that research performed at the STVHCS also requires approval by the STVHCS R&D Committee. If I have questions or concerns, I am encouraged to contact the STVHCS Research Office or the UTHSCSA Office of Clinical Research. I also understand that performing tasks beyond this scope of practice, without specific authorization, may lead to disciplinary action. Both the principal investigator and I are familiar with all duties and procedures granted in this Scope of Practice. I agree to abide by the parameters of this Scope of Practice and all-applicable hospital policies and regulations.

Discussion and Questions

The Informed Consent Process

Robin Tragus, RN, MSN
Anne Leonard, MPH, RN
Karen Aufdemorte, BA, HT
Erika Hess, BA, MS
Lillian Sanchez, MSN, RN
Eleanor Montalbo

Informed Consent

Robin Tragus, MSN, RN, CCRC, CDE

Pediatric Research Operations Manager,
UT Health Science Center at San Antonio

Manager,
Children's Health Advocacy Research & Treatment Center
CHRISTUS Santa Rosa Children's Hospital

Objectives

- Explore the Informed Consent Process
- Examine some potential pitfalls in obtaining consent

Historical Context for Current Regulatory Environment Surrounding Informed Consent

- Reaction to abuses which occurred as a result of research on human subjects
  - Nazi Germany
  - Tuskegee
  - Willowbrook
- Highly publicized recent cases
  - Jesse Gelsinger
  - Ellen Roche

Informed Consent Scenarios

Scenario 1:
How not to obtain Consent and Assent

So What Went Wrong?

- Was it informed?
- Was it consent?
- Was there assent?

Issues with the process as presented

- Procedural:
  - Study procedures performed before obtaining consent
  - Did not provide adequate time to think about being in a study
  - Consent document not read
  - Witness signing without witnessing
  - No copy of document given to parents

Issues, continued

- Lack of understanding on the part of parents and participant what was involved in study participation
- Lack of understanding on the part of the parents about risks
- Investigator not around to answer questions
- Coordinator did not ascertain level of understanding
- No mention that participation is voluntary, and can be discontinued at any point

Issues, continued

- No discussion that this is **research**
  - Therapeutic misconception
  - Not all products are FDA approved
  - No discussion of randomization and related issues
- Lack of agreement between parents about participation

Food for thought

- Conflict of interest?
  - Pressure to enroll
  - Financial aspects
    - For parents
    - For investigator

What should have happened?

Scenario 1 revisted

What was different?

- Ample time to think about participation
- Environment conducive to asking questions
- Discussion of risks of participation

Other issues that must be addressed:

- Honest explanation of alternatives to participation
- Thorough discussion about study procedures and timelines
  - Will improve compliance of participants
  - Cuts down on early termination

Issues related to obtaining consent involving a second language

Scenario 2

Subtitles for Non Spanish Speakers

- Mr. Participant: [What did she say?]
- Mrs. Daughter: [They are going to give you a medicine for blood pressure, and it's going to make you feel good.]
- Mr. Participant: [What did she say?]
- Mrs. Daughter: [The nurse said, don't worry, everything will be fine.]
- Mrs. Daughter: [Dad, do you have any questions?]
- Mr. Participant: [What do you think I should do?]
- Mrs. Daughter: [Just sign the paper.]

What went wrong?

- Daughter heard the work "placebo" and didn't understand it, or misheard it, so translated it as a word that sounded similar but had an entirely different meaning
- Concept that study is research was not conveyed
- Daughter was uncomfortable discussing "impotence", so she edited and substituted
- Subject has no idea what he has agreed to do

Suggestions for how it could have been done:

Scenario 2 Revisited

What was different?

- Bilingual health professional providing translation
  - Not a family member
- Provided opportunity for subject to hear about entire study including risks in an unedited fashion
- Provided way for subject to have information read to him in an impartial manner

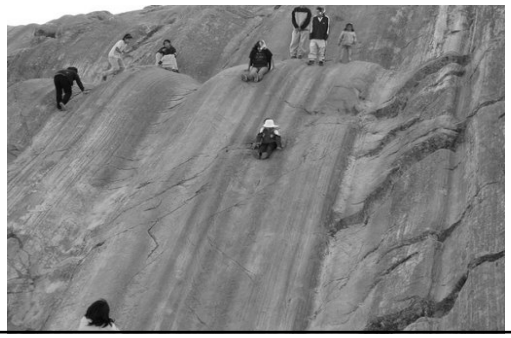
Lessons learned

- Know your potential population
- Be prepared
  - Plan from before you start the study how you will do the informed consent process
    - Form C (questions 4b- especially item 7)
    - Form J
    - Form W
  - Have a consent translated very soon after approval of English consent
    - Form H-1

Resources

- http://research.uthscsa.edu/irb
- http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm
- http://www.fda.gov/cder/index.html
- http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page2
- http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php

A Slippery Slope



Data Safety Monitoring Plan

Kimberly Summers, PharmD
STVHCS Research
and Development

Developing Your Protocol Specific Data and Safety Monitoring Plan

Kimberly Summers, PharmD
Assistant Chief for Clinical Research
South Texas Veterans Health Care System
Research and Development Service

Overview

- What is a Data and Safety Monitoring Plan (DSMP)
- Why is a DSMP required
- Components of a DSMP
  - Assignment of the level of risk
  - Who, what, how the monitoring happens
  - AE reporting mechanism
    - Grading and attribution
    - What, to whom, and within what timeframes
- Reporting of the DSMP and Action plan

What is a DSMP?

- A written plan and process
- Individualized to the study
- Developed in regards to the study purpose and design
- Prospectively defines the methods to be used by the Sponsor, PI and study team to oversee safety of study participants
- Involves on-going evaluation of study data
- Ethical responsibility of the study investigators to their participants

Data and Safety Monitoring Plan (DSMP) VS Data Safety and Monitoring Board (DSMB)

Data and Safety Monitoring Board (DSMB)

- Independent committee formed to monitor data with respect to safety and treatment
- Formed for
  - High risk studies
  - Larger, single or multi-center, clinical trials
- Required by NIH for all Phase III studies
- Studies which include an established DSMB by an external entity still require a local DSMP

Local PI Responsibilities

- DSMB
  - Limited to collecting information and forwarding to DSMB for analysis
  - Implementing local actions based on DSMB analysis if needed
- DSMP
  - Capturing and collecting data
  - Monitoring collected data
  - Interpretation and analysis of collected data
  - Reporting results of analysis
  - Implementing actions based on analysis if needed

Why DSMPs Now?

- Society and government have lost confidence in the ability of investigators and scientific community to police itself
  - Result of several high-profile cases
  - Scientific community slow to acknowledge scope and magnitude of problem
  - Intensive auditing identified substantial non-compliance

USA Today February 27, 2001

- **Poor oversight puts research subjects at risk**
  - "Government system to support participants falls short"
  - "..oversight is so disorganized that no even knows…how many participating patients are injured or killed."
  - "..close to pitiful, and is surely not enough to counteract the temptation by researchers to bend the rules."
  - "…patients will remain at the mercy of universities, hospitals and doctors who have more on their minds then your health."

Washington Times Article June 17, 2008

- VA testing drugs on war veterans: Experiments raise ethical questions
  - "government is testing drugs with severe side effects…using small cash payments to attract patients"
  - "VA took three months to alert its patients about severe mental side effects"
  - "VA's behavior in the anti-smoking study violated basic protections for humans in medical experiments"

Studies Which Require a DSMP

- All studies considered to be more than minimal risk
  - Involve high risk populations and/or high risk therapies
- Multi-site research where UTHSCSA is the coordinating site
- Studies where there is an NIH or FDA requirement for a plan
- Studies when requested by the IRB

Initial and Continuing IRB Review

- Initial IRB approval
  - Research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects
  - IRB must review the DSMP in the protocol developed by the investigator
    - DSMP needs to include procedures for reporting adverse events (AEs)
- Continuing IRB approval
  - The investigator must submit to the IRB a written progress report that includes:
    - Information that may impact on risk benefit ratio: summary of AEs and unanticipated problems
    - An assurance that all AEs and unanticipated problems have been reported as required
    - DSMB reports if applicable

38 CFR 16.11(a)(6) & VHA 1200.5§7(a)(6)
VHA 1200.5§7(g)

Bending Over Backwards To Meet Regulatory Requirements

Fostering an Ethically Sound Research Environment

- Protects rights and well-being of human subjects
- Assures accurate & verifiable data collected according to protocol
- Preserves the public trust in the integrity and quality of research carried

DSMP SHOULD BE COMMENSURATE WITH THE LEVEL OF RISK AND WITH THE SIZE AND COMPLEXITY OF THE STUDY

One Size Does Not Fit All…

Level of Monitoring

Minimal risk, single site, low number of participants

PI monitoring at regular intervals (i.e. during continuing review)

Greater than minimal risk, multiple-sites, high number of participants

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

Determining Level of Risk

- IRB determines the level of risk based on the component analysis completed on Form C of the IRB submission

6. Research Plan / Methods:

a. Description of Methods – Provide a comprehensive narrative describing the research methods. Provide the sequence of events for conducting the research and a description of the methods used to protect privacy during the study.

Describe here or CUT AND PASTE from sponsor's protocol or grant application

b. List of Research Procedures or Components (Components can be two or more procedures) (Click here for example)
(add rows or delete unused rows) (Consider as one component, multiple procedures that may lend themselves to having identical risks and benefits described in a single table in c, although exceptions exist to this guidance.)

	Note that:	A	*	B	*	C
#	Research components	Local Standard Practice required by the research plan		Research Only (Indicate # performed solely for research (research only) or indicate # performed outside frequency or timing for acceptable local practice)		Total Number of Research Related Procedures
1						

c. Risk-Benefit Analysis
For each research procedure identified in section 6b above, complete a risk-benefit analysis table
(Two tables are provided, copy and paste additional tables as needed)

Considerations for Determining Level of Risk and DSMP Design

- Study Phase
  - Phase I and II
    - Small number of patients and short duration
    - High risk or special populations may require additional monitoring
    - Independent review may not be necessary
  - Phase III
    - DSMB required by NIH
    - Number of subjects and sites increase
    - Increased numbers of subjects are exposed to interventions
    - More frequent and more rigorous reviews needed for local DSMP

Considerations for Determining Level of Risk and DSMP Design

- Regulatory Considerations
  - Pivotal studies for INDs require increased monitoring
- Trial Design
  - Randomized, controlled, clinical trials require review of the data both aggregate and by treatment group
- Disease/Syndrome under Investigation
  - High risk and special populations require additional monitoring
  - Increased monitoring may be required for serious and/or life threatening diseases when endpoints are anticipated to occur frequently

Considerations for Determining Level of Risk and DSMP Design

- Study Population
  - Plan should include monitoring of recruitment, enrollment, and retention activities
- Study Intervention
  - Frequency and intensity of monitoring should take into account safety of treatment, indication for use, dosing level and frequency, presence of comorbid diseases, and time on study drug
- Endpoints / Outcome Variables
  - Type and frequency of monitoring will be dependent on the subjects' time on study intervention and time from baseline to final follow-up

Who is Monitoring?

- Always principal investigator (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

Team Effort

Responsible Party at Each Step of Safety Monitoring

(2) Responsibilities
Who will be responsible for safety monitoring? *(Select all that apply)*:

Responsible Party:	Role:	Collection	Compiling Reports	Analyzing/ Assessment
☐	The Principal Investigator	☐	☐	☐
☐	Other Research Team members (e.g., Co-PI, Research Coordinator, etc.)	☐	☐	☐
☐	An independent monitor from this institution **(internal).** **Name:**		☐	☐
☐	An independent monitor from institution/sponsor **(external).** **Name:**		☐	☐
☐	A data and safety monitoring board (DSMB)**, an independent DSMB or a data safety monitoring committee (DSMC). **Name of DSMB/C:** **Location of the DSMB/C):**		☐	☐
☐	Other (describe):	☐	☐	☐

If PI is sole safety monitor of the study, explain how conflict of interest will be mitigated: ☐ N/A

What is Being Monitored?

- 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…

Monitoring Focus

- Collective trends from individual participants which may show that participation in the trial has become too risky
  - Adverse events (AEs)
  - **AEs occurring more frequently or with increased severity than anticipated may need to be considered a UPIRSO**
  - Time frames for reporting
- Stopping rules (safety and efficacy)
  - Unblinding procedures if applicable
- Interim Analysis (plans, if applicable; specified in protocol)
- Developments which may change the risk-to-benefit ratio
  - If risk-to-benefit ratio changes when should the study be:
    - Changed?
    - Suspended?
    - Terminated?

Adverse Event Reporting

- Plan should define and clarify
  - Adverse event (AE)
  - Unanticipated problem involving risk to subject or others (UPIRSO)
  - Serious adverse event (SAE)
- Plan for grading toxicities
- Plan for assessing relationship to study enrollment or investigational drug

Assessing Severity of AEs

- Grading severity from 0-4 or 1-4
- Examples
  - WHO Toxicity Criteria
  - Common Toxicity Criteria (CTC)
  - Radiation Therapy Oncology Group (RTOG)
  - Division of AIDS Toxicity Grading Table

Assessing Relationship of AEs

- Probable
  - Strong relationship
    - AE abates upon discontinuation of the investigational product and recurs with the same characteristics after readministration
- Possible
  - Equally valid arguments can be considered for or against an implication of the investigational product
- Unlikely
  - There are good reasons to think that there is no relationship
    - AE is a known adverse drug reaction of a concomitant medication, and/or the same AE does not reappear after readministration of the investigational product

Integration of Monitoring Entities

- As part of the DSMP provide information on entities involved in safety monitoring
  - Local medical monitor
  - Local data and safety monitoring boards/committees
  - External medical monitors
  - External safety monitors
  - External data and safety monitoring boards/committees
- Explain how all monitoring entities will be integrated

Data Integrity as Part of the DSMP

- Explain how and when data will be reviewed to ensure accuracy
  - Protocol deviations
  - Queries generated and outstanding
  - Internal quality management review
  - Comparing source documents to CRFs

Reporting of DSMP Review

- PI compiles a brief evaluation summary
  - If the evaluation of the aggregate data reveals an UPIRSO
    - PI must forward to local IRB
    - UPIRSO form must be attached explaining how the evaluation constitutes a UPIRSO
  - If the evaluation does NOT reveal an UPIRSO
    - PI must forward to local IRB a summary of all evaluations as part of continuing review at least annually

Conclusions

- Elements of a DSMP
  - Assignment of the level of risk in the particular study
  - Who, what, how the monitoring happens
  - The AE reporting mechanism
    - Including grading and attribution
  - What, to whom, and in what timeframe do events get reported.
- DSMPs are a mechanism for planning for research participant safety and the success of your study

Worth it in the End

Data Integrity

Dawn Lantero, PhD
Research Subject Advocate

CONDUCTING CLINICAL RESEARCH: DATA INTEGRITY

Dawn A. Lantero, Ph.D.
Research Subject Advocate
Institute for Integration of Medicine & Science (IIMS)
University of Texas Health Science Center San Antonio
November 13, 2008
lantero@uthscsa.edu

Regulatory Requirement

- "An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting documents . . . "

--21 CFR 312.62(b) Investigator recordkeeping and record retention

Good Clinical Practice (GCP)

- Following GCPs ensures accuracy and reliability of data generated during course of clinical trial. Compliance with GCPs will ensure:
  - The rights and safety of human subjects are not compromised
  - Appropriately and adequately trained staff manage the study
  - The study is carefully documented
  - Protocol is strictly followed

http://www.ich.org/LOB/media/MEDIA482.pdf
Dunn & Chadwick (1999)

IRB Form R

- Form R: Human Use Research Monitoring Participant Safety and Data Integrity
  http://research.uthscsa.edu/irb/forms_A-Z.shtml

Science and Truth

- Truth is knowing how everything works at all times under all conditions
  - Certainty = Law (e.g., Law of Gravity)
  - Not Certainty = Theory/Hypothesis
- People (e.g., scientists, philosophers, parents, etc) are trying to discover Truth

Hergenhahn (1992)

Methods to Discovering Truth

UNSCIENTIFIC METHODS

- Tenacity
  - cling to beliefs despite lack of supporting evident
- Intuition
  - common sense
- Authority
- Rationalistic Method
  - reasoning
- Empirical Method
  - objective observations

SCIENTIFIC METHOD

- Step 1: Defining and Delimiting the Problem
- Step 2: Formulating the Hypothesis
- Step 3: Gathering the Data
- Step 4: Analyzing the Data
- Step 5: Interpreting the *Results*

Thomas & Nelson (2001)

Validity and Reliability

VALIDITY

- Definition: degree to which test/instrument measures what is it designed to measure
- Types
  1. Logical: involve what is to be measured
  2. Content: adequately samples course content (education)
  3. Criterion: related to recognized standard/criterion
  4. Construct: measures hypothetical construct

RELIABILITY

- Definition: consistency, or repeatability, of measure
- Observed = True + Error
- Sources of Error
  1. Participant
  2. Testing
  3. Scoring
  4. Instrumentation

Thomas & Nelson (2001)

Sources of Error: Participant

- Definition: Error generated by participant through action or inaction (participant compliance), although could be influenced by others
- Examples
  - Hawthorne Effect
  - Mood: "bad day"
  - Motivation:
  - Fatigue: physically unable to perform activity
  - Misunderstanding instructions
  - Missing appointments: forgetting (illness; disorganized), transportation
  - Feelings of being overwhelmed: illness, complicated protocol
  - Language: medical lingo, another language

Thomas & Nelson (2001)
Morse, Simon, Coburn, Hyslop, Greenspan & Balson, (1991)
Butler (2007)

Sources of Error: Testing

- Definition: Error generated by researcher when executing/running/giving the test
- Examples
  - Lack of clarity or completeness of directions given to participant
  - Amount of adherence to instructions of protocol
  - Addition of supplementary directions or motivation to other researchers/participants
  - Environment perceived by participant as "comfortable" or "uncomfortable"

Thomas & Nelson (2001)

Sources of Error: Scoring

- Definition: Error generated by researcher when scoring the test/recording data
- Examples
  - Carelessness and inattentiveness
  - Lack of competence, experience and/or dedication of the scorers/recorder
  - Incomplete source documentation
  - Inaccurate recording on Case Report Form (CRF) or transferring of data to electronic system

Thomas & Nelson (2001)

Sources of Error: Instrumentation

- Definition: Error generated by instrumentation; ultimately, researcher is responsible
- Examples
  - Lack of calibration of mechanical and electronic equipment
  - Insensitivity to variable of interest
  - Mechanical malfunction
  - Low batteries

Thomas & Nelson (2001)

Quick Review

- 4 sources of error that compromise reliability of data
  1. Participant
  2. Testing
  3. Scoring
  4. Instrumentation
- Reliability (Observed = True + Error) → Validity → Scientific Method → Truth

Sources of Errors & Proposed Solutions

1. Participant (locus of control: participant)
   a) COMMUNICATION
      1. Make eye contact
      2. Use participant's name
      3. Be honest
      4. Be supportive
   b) Respect
      1. Privacy
      2. Time management
      3. Be accessible
   c) Handout from Susan Lowell Butler
   d) Butler (2007)

Morse, Simon, Coburn, Hyslop, Greenspan & Balson (1991)
Theiden , Philipsen, & Wulf (2006)

Sources of Errors & Proposed Solutions

2-4. Testing, Scoring, Instrumentation (locus of control: Researchers; ultimately: PI)

a) Training
   1. " . . . study was performed on the premise where the participants were doing the study for us and not vice versa." (Theiden, Philipsen, & Wulf , 2006, pg. 97)
   2. Know & follow the protocol: "The investigator of a study is required by law to conduct the study according to the: investigational plan (including the protocol and the IRB stipulations) . . ." (Dunn & Chadwick, 1999, pg. 44)
   3. Follow instructions for testing instruments/assessments
   4. Practice, practice, practice
   5. Scope of Practice duties only (HOP 7.2.3; http://research.uthscsa.edu/ocr/ScopeofPracticeStudyForm.pdf)

Sources of Errors & Proposed Solutions

- 2-4. Testing, Scoring, Instrumentation (locus of control: Researchers; ultimately: PI) con'd
  - b) Data & Safety Monitoring Plan
    1. Examples: internal/external monitor; DSMB/C; Form R
    2. Considerations (Form R)
       - a) 21 CFR 56.111 (6); 45 CFR 46.111 (6); VHA Handbook 1200.5
       - b) How will data integrity be assessed?
       - c) When will data integrity be assessed?
       - d) Who is responsible?
       - e) If there are other monitoring entities, how will these activities be integrated?

Proposed Solutions: Other Resources

- Any presenter from today
  - Office of Clinical Research
    - Director: Holly Nolan, MS
  - IRB
    - Director: Joseph Schmelz, PhD, RN, CIP
    - Associate Director: Roy Estrada, PhD, PA-C, CIP
  - VA
    - Associate Chief of Staff for Research: Peter Melby, MD
    - Research & Development: Kim Summers, PharmD
  - Office of Regulatory Affairs
    - Manager of Clinical Study Monitors: Anna Taranova
    - ComplianceLine Hotline 1-800-500-0333
  - Research Subject Advocate: Dawn Lantero, PhD
- Dr. Jenice Longfield, Assistant Vice President for Research Operations (210) 567-0651 longfield@uthscsa.edu
- HOP 1.3.6 Vice President for Research
- HOP 7.2.1 Human Research Protection Program (HRPP) Responsibilities
- HOP 1.6.6 Institutional Review Board
- HOP 7.2.2 Institutional Review Board Responsibilities
- Complaints Policy & Procedure
- Noncompliance Policy & Procedure
- Office of Regulatory Affairs & Compliance
- VHA Handbook 1200.5

Wrap Up

- Data are the integral part of any research when following the Scientific Method in quest for Truth
- Reliability: Observed = True + Error
- Data not reliable due to participant, testing, scoring, and/or instrumentation errors, then
  - GCP not followed
  - Violating scientific method
  - Invalid results → no benefits for study (Belmont Report) → put participants as risk for no reason

ANY QUESTIONS?

References

- Butler, S.L. (2007). Clinical research: A patient perspective. In J.I. Gallin & F.P. Ognibene (Eds.), *Principles and Practice of Clinical Research, 2nd ed. (pp.143-153).* Amsterdam: Elsevier Inc.
- Dunn, C.M., & Chadwick, G. (1999). *Protecting Study Volunteers: A Manual for Investigative Sites.* Boston: CenterWatch, Inc.
- Hergenhahn, B.R. (1992). *An Introduction to the History of Psychology, 2nd ed.* Pacific Grove, CA: Brooks/Cole Publishing Company.
- The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (http://www.ich.org/LOB/media/MEDIA482.pdf) .
- Morse, E.V., Simon, P.M., Coburn, M., Hyslop, N., Greenspan, D., & Balson, P.M. (1991). Determinants of subject compliance within an experimental anti-HIV drug protocol. *Social Science & Medicine, 32*, 1161-1167.
- Theiden E., Philipsen, P.A. & Wulf, H.C. (2006). Compliance and data reliability in sun exposure studies with diaries and personal, electronic UV dosimeters. *Photodermatology, Photoimmunology, & Photomedicine, 22*, 93-99.
- Thomas, J.R. & Nelson, J.K. (2001). *Research Methods in Physical Activity, 4th ed.* Champaign, IL.: Human Kinetics:

Documentation: The Essential Regulatory Documents

Lillian Sanchez, MSN, RN

Documentation: The Essential Regulatory Documents

- Lillian L. Sanchez, MSN, RN
- Office of Clinical Research
- UT HSC
- "Conducting Clinical Trials"

1

OBJECTIVES

- List the essential documents that must be maintained during the conduct of Human Subject Research
- Become aware of the securing and retention practice of research records
- Describe "Good Documentation Practice"
- Knowledge that this practice will lead to "Good Clinical Practice" in research

2

What is a Regulatory Binder?

- **A binder containing the essential regulatory documents for the conduct of a clinical trial**
  - Protocol specific information
  - Regulatory requirement documentation
  - All study related correspondence

3

Purpose of Essential Regulatory Documents

1. **Serve to maintain and communicate information that is essential for:**

   the compliance of the institution, investigator, sponsor, CRO and monitors, with all regulatory requirements

4

Purpose of Essential Regulatory Documents

2. Assist in the management of the trial – Staff has access to protocol information and procedures

3. Make available the documents that are essential for audits by sponsors or inspections by regulatory authorities.

5

Purpose of Essential Regulatory Documents

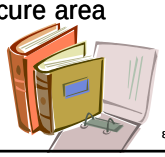
4. Allow for the evaluation of:
   A. The conduct of the trial
   B. The integrity of the data

6

7

Important!!!

- All clinical trials must have a regulatory binder at the time of the study start-up
- Keep all original and revised documents
- Do not start the study without IRB approval
- Most important: Select a secure area



8

Regulatory Binder Organization

- Set up SOPs in your department for document organization: who, what, when, where and how
- Arrange binders as per sponsor requirements
- Make your own if not specified or if it is Sponsor-investigator initiated study

9

Regulatory Binder Organization

- You may need more than one binder
  - make note in main binder of additional binder(s)' existence
- Use tabs to organize sections
- Place in chronological order and most recent on top

10

Documents Maintained

- Preparatory documents and correspondence
- Study/trial documentation and correspondence
- Closing/end documentation and correspondence

11

Preparatory Documents

- Investigator and Research Staff
  - Educational qualifications, current Curriculum Vitae (CV), licensure, Research Scope of Practice Form
  - Training records
  - Financial disclosure forms ; conflict of interest management plans

12

Preparatory Documents

- Proposal Documentation as applicable
  - FDA 1571 (Sponsor Investigator IND)
  - FDA 1572
  - Research Agreements, Financial agreements, Certificate of Proposal, Clinical Trial Agreements
  - Proposal/Planned Research Activities

13

Preparatory Documents

- Institutional Review Board
  - Application Protocol - Submission Documents (Go to OIRB website for latest policy and forms)
    - All Information to be given to participants
      - Advertisement and planned compensation
      - Screening/recruitment scripts
      - Informed Consent plans and documentation
      - Educational material for the participant

14

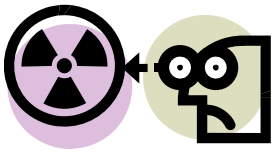
Preparatory Documents

- Institutional Review Board
  - Application Protocol - Submission Documents
    - Include investigative tools/questionnaires and description of all planned interventions
    - Safety monitoring plans
    - Copies of Case Report Forms to be used
    - Investigator brochure/manual of test article
  - Emails, letters to and from the OIRB
  - IRB Approval Letter

15

Preparatory Documents

- Other approval documents
  - Radioactive Drug Research Committee
  - Radiation Safety Committee
  - Institutional Biosafety Committee
  - Affiliate Research Review Unit approval



16

Preparatory Documents

- Procedures, Study Manuals
- Delegation of Authority/Signature Logs
- Extra Blank forms: e.g., questionnaires CRFs, test article order forms and test article accountability forms
- Study plan including also: schedules, budget billing grids

17

Study in Progress Documentation

- **All Continued IRB Communication:**
  - **Related to ongoing research:**
    - Protocol modifications and amendments
    - Reports to the IRB: e.g., Continuing Reviews, UPIRSOs
    - Changes in the information given to participants/consents
    - Changes in research team members
    - Communication to and from the IRB

18

Study in Progress Documentation

- Keep all versions of all IRB submitted documents
- **Use only IRB approved** documents with participants
- Maintain in chronological order keeping the latest version on top
- Keep most recent IRB approved Informed Consent form in a plastic sleeve.

19

Study in Progress Documentation

- **Study Logs**
  - Investigator and Team delegation of authority log
  - "On call" log with contact information
  - Site Signature log
  - Training logs/training certificates

20

Study in Progress Documentation

- **Study Logs Cont'd:**
  - Master Subject and Screening logs: chronological tracking of enrolled and screen failed
  - Subject Identification Code List/procedure
  - Log for tracking all adverse events

21

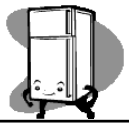
Study in Progress Documentation

- Study Logs Cont'd
  - Equipment logs: calibration, repair, and or QA logs
  - Records/logs of specimen/tissue samples; include shipment information
  - Clinical Monitor site visit logs

22

Study in Progress Documentation

- Refrigerator/Freezer Logs
  - Maintain the appliance in a secure area
  - Assign staff and list
  - Provide Temperature Parameters and an appropriate thermometer for the appliance
  - Documentation: Date, Time, Initials/signature, Actual Temperature, Problems and how they were resolved, by whom



23

Study in Progress Documentation

- **IND Safety Reports**
- **Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO) for Serious Adverse Events Reports**
- **Event tracking log for non-adverse and all adverse events**

24

Study in Progress Documentation

- Related to Drug/Device Inventory:
  - Instructions for handling
  - Receipt and Shipment logs
    - Keep extra supply reorder forms
  - Accountability logs: Inventory, Dispensing, Disposition

25

Study in Progress Documentation

- Drug receipt/dispensing/return logs should list:
  - Dates received, dispensed or returned (check against manifest)
  - Persons receiving, dispensing or returning (note condition of the article)
  - Accurate number of kits, number of packages or containers per kit, number of tablets or drug per container or kit, dosages of each
  - Lot or batch numbers

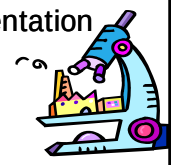
26

Essential Documents
(ICH GCP, FDA)

- **Related to Drug/Device cont'd**:
- The PI is Responsible for the Test Article
  - Drug logs may be kept in pharmacy (keep a copy and meet to reconcile at least weekly)

27

Study in Progress Documentation



- Medical/Laboratory/Technical Procedures/Tests :
  - Laboratory Certification Requirements
    - required by Clinical Improvement Act (CLIA)1988 Updated 2003) issued by accreditation organizations such as College of American Pathologists (CAP), COLA (formerly Commission on Office Laboratory Accreditation)
    - CV of Laboratory Director
    - Established quality control and/or external quality assessment or other validation (keep records)

28

Study in Progress Documentation

- Medical/Laboratory/Technical Procedures/Tests Cont'd:
  - Normal Values/Ranges
  - Analysis Reports: PI initials and dates reports. PI documents actions taken for clinically significant test values

29

Study in Progress Documentation

- **General Correspondence**
  - Letters and Memoranda
  - Written documentation of telephone conversations with sponsors
  - Facsimiles
  - Electronic communication between sites, monitors, sponsors and other trial related groups

30

Study in Progress Documentation

- **Participant Files**
  - Original Signed Informed Consents
  - Documentation of Informed consent process
  - Copies of executed case report forms (CRFs)
  - Source documents, copies of source documents (note location of originals)
  - Individual visit/procedural notes
  - Individual Calendar of Events-visit schedule

31

Closure Documentation

- Final Report to the IRB
- Closure documents and correspondence with the Sponsor
- Disposition of test articles

32

Other Important Documents

- Financial Records
  - Account for charges: Start amounts, used amounts, and receipts
  - Reflect charges on source documents
  - Know current laws related to billing for standard of care in research activities

33

Electronic Data
Title 21 CFR 11

Guidance for Industry Computerized Systems Used in Clinical Investigations
FDA May 2007

34

Electronic Records
External and Internal Safeguards

- 21 CFR 11 Specific Processes Required: SOPs, limited access, audits trails, automatic date and time stamp and training
  - For electronic records and signatures ensure accuracy, reliability, consistent performance and security
  - Program must independently record date, time, and signature in all entries and actions that create, modify, or delete

35

Retention/Archival

- Follow UT HSC Policy HOP 2.2.1
- Always keep for the longer time frame requirement if there are multiple agencies' requirements

36

Don't keep just the skeletons!

- What you don't keep or how you keep what you have can come back to haunt you!
- The body of your work supports the study

37

Retention/Archival

- NIH- 3 years after the final financial report and all other records/documents per grant
- NSF- retain for at least 3 years
- HHS- IRB retains records for at least 3 years after completion of research. The PI retains signed subjects ICF for at least 3 years after study completion

38

Retention/Archival

- FDA 21CFR312.62 (DRUG)
  - 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated
  - or, if no application is to be filed or if the application is not approved for such indication, keep for 2 years after the investigation is discontinued and FDA is notified.
  - FDA may require longer

39

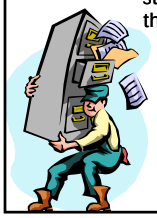
Retention/Archival

- FDA 21 CFR 812.140 (DEVICE)
  - 2 years after the latter of the following two dates:
    - The date on which the investigation is terminated or completed,
    - or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
    - FDA may require longer time frame for retention

40

Retention/Archival

- FDA:
  - The investigator may withdraw from the responsibility to maintain records and transfer custody of the records to another faculty or staff person who will accept responsibility for them.
    - Notice of a transfer must be given to the FDA no later than 10 working days after the transfer occurs. **A copy of that notice should also be sent to the IRB.**



41

Retention/Archival

- UT HSC
  - UT HSC HOP 2.2.1
  - HIPPA
  - Funding source

  Primary:
    - State of Texas Record Retention Schedule for HSC
      - Access Records Management at HSC Library for most current schedule

42

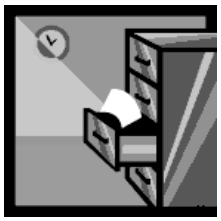
Retention/Archival

- **What is the definition of a state record? Are all records at the UTHSCSA considered state records?** A state record is any written, photographic, machine-readable or other recorded information created or received by or on the behalf of a state agency or elected state official that documents activities in the conduct of state business or use of public resources Keep 15 years

43

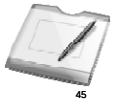
Retention/Archival

- VA Retain for 5 years
- Notify the office of Research and Development
- Refer to VA Policies



Documentation

- Must be:
  - Legible (not legible = what happened?)
  - Timely – At time of event
  - Accurate
  - Consistent (CRFs with Source Documents; dates of events)
  - Remember "If not documented it did not get done."
  - Accountable (Who entered what)



45

Documentation

- Informed Consent Form
  - Use IRB templates;
  - STVHCS use IRB/VA template
  - Fill in the blanks appropriately
- Right Persons Sign It, Time and Date It
  - Subject or guardian
  - Proper Research Team Member, impartial witnesses
- Dates and times are consistent for all and written at the time of signature.

46

Documentation

- Document the Informed Consent Process
  - "Research Consent/Enrollment Note Includes:
    - The Names of: Study, the PI, person obtaining consent; person signing for participant if other than participant
    - Statements that: the study was explained to the participant (surrogate); that participant (surrogate) signing was capable of understanding the consent process; participant was given opportunity to ask questions and your response; that a copy of ICF was given to the participant as well as contact information for concerns or questions

47

Documentation

- Ascertain Progress Notes Include:
  - The Research Procedures, treatments or interventions that may impact a patient's medical care
  - Research procedures/results used that are standard of care
  - Indications for this study treatment and potential risks (physical/psych); possible drug interactions and or toxicities
  - Instructions given and "teach back" by subject

48

Corrections

- Draw **one line** through the error, write the correct information, initial and date
- Corrections to CRFs, in general should be done only by:
  - The person that recorded the error
  - Those authorized in the delegation of authority document: Investigator, Research Nurse, Research Coordinator

49

Corrections

- NOTE: Corrections to **source documents** should be done only by the person that recorded the error:
  - A straight line is drawn through the error, the correction is made, initialed, and dated.
  - Notation or addendum may be necessary to clarify why correction is made. Explanation is needed if late entry was made or if another person corrects
  - *Throw Away White Out solutions!*

50

References

- UT HSC Handbook of Operating Procedures Chapter 2
- Record Retention Schedule: http://www.library.uthscsa.edu/university/rrsSearch.cfm
- FDA Title 21: CFR 11; CFR 312; CFR 812;
- Guidance for Industry Computerized Systems Used in Clinical Investigations FDA May 2007
- HHS Title 45 Part 46
- International Conference on Harmonisation E 6 *Guidelines Good Clinical Practice* Chapter 8: Essential Documents for the Conduct of a Clinical Trial
- VA Handbook 1200.05

51

Study Drug Accountability

Jennifer Hillman, PharmD
Scott Soefje (CTRC), PharmD
Virginia Doyal (VA), PharmD, BCPS

Study Drug Accountability University Health System

Jennifer Hillman, PharmD

UHS Research Department Points of Contact

Evelyn Swenson-Britt, MS, RN
Clinical Research Director
Magnet Project Director
4502 Medical Drive
Mail Stop 96-1
San Antonio TX 78229-4493
Phone: 210-358-4176
E-mail: evelyn.swenson-britt@uhs-sa.com

Joan Thomas RN, MSN
Clinical Research Cordinator, UHS
Research Department
4502 Medical Drive
Mail Stop 96-1
Phone: 210-358-0026
Fax: 210-358-8496
E-mail: joan.thomas@uhs-sa.com

Department Website: http://www.universityhealthsystem.com/Research/Research_Department_Home.htm

UHS Inpatient Pharmacy Points of Contact

- Jennifer Hillman, Research Pharmacist
  Phone 358-0418 jennifer.hillman@uhs-sa.com
- Beverly Miller, Research Technician
  Phone 358-1087 beverly.miller@uhs-sa.com
- Javier Palacios, RPh Research Supervisor
  Phone 358-0398 javier.palacios@uhs-sa.com
- Jimmy Sanchez, Technician weekend coverage
  Phone 358-2900

When contacting pharmacy please be sure to speak with someone live on the phone rather then leaving a message

UHS Pharmacy Capabilities

- Hours of Operation: 24 hours per day/ 7 days per week
- Room temp, refrigerated and frozen
- All Dosage Forms

Fee Structure

- Before submitting a budget to the sponsor, ensure that pharmacy charges are included.
- A financial supplement will be sent to you from the UHS research department
  - Includes the fee structure from the various necessary departments
  - Sign and return to UHS research department
  - Assigned project number

Order Sets

- Inpatient
  - Inpatient order sets are to be developed by the Research Coordinators
  - Order sets will be delivered to the UHS Research Department when submitting the research protocol
  - Once the research department has received the signed financial supplement it will forward the orders to Allyson Clark who will enter the information on SunRise
- Outpatient
  - Created by inpatient pharmacy
  - Coordinate with UHS inpatient pharmacy to ensure order sets are available prior to patient enrollment
  - Provide a hard copy or fax of the order to inpatient pharmacy for record of dispensing

Monitor Visits

- Unannounced monitor visits may not be accommodated
- Contact inpatient pharmacy at least 2 weeks in advance to set up appointment.

Education

- Pharmacy requires education either from the drug company or the clinical study coordinator prior to beginning a research study
- We will **NOT** start a study if the pharmacy department has not been given appropriate direction
- If there are changes or amendments to the protocol please provide a copy to pharmacy
- Keep pharmacy informed of any direct changes to the study drug and ensure that pharmacy is aware of how the change will effect overall procedures

Study Binder

- Tab 1 UHS approval letter
- Tab 2 IRB approval letter
- Tab 3 Key personnel with contact information
- Tab 4 study protocol with amendments
- Tab 5 Informed consent
- Tab 6 Sample order form/IVRS worksheets
- Tab7 Drug accountability
  - Shipping receipts/faxes/
    - Date/time/quantity/lot #/strength

Study Binder

- Tab 8 patient specific drug accountability
  - Subject name
  - Subject study number
  - Subject mrn number
  - Date dispensed
  - Dose/quantity dispensed
  - Lot # / expiration date
  - Date retuned (if applicable)
  - Initials of person dispensing
- Tab 9 drug destruction records

Study Drug Delivery

- All investigational study medication dispensed to patients enrolled at UHS must be shipped DIRECTLY to UHS inpatient pharmacy

Study Drug Dispensing

- When picking up research medications staff must be properly identified with name badge
- All medication will be logged out of pharmacy using a designated research record for dispensing

Study Drug Returns

- Record the amount returned
- Pharmacy will perform a double count and log the returned medication
- Pharmacy will store all the returned medication until the monitor gives final approval for proper destruction

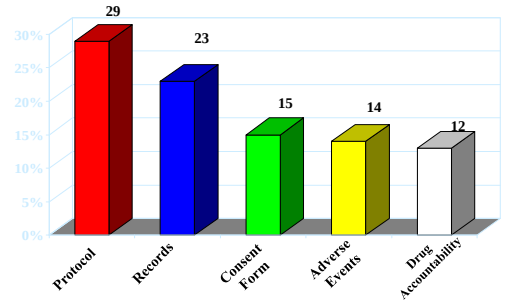
Drug Accountability in Clinical Research

Scott Soefje, Pharm. D., BCOP
Investigational Drug Section
CTRC @ UTHSCSA
San Antonio, Texas

Investigator Responsibility

- **FDA regulations require investigators to establish a record of the receipt, use and disposition of all investigational agents**
- **Part of FDA 1572 responsibilities**
- **This responsibility may be delegated**
- **The intent is to assure that drug product is used only for patients enrolled on an approved clinical trial**

Clinical Investigator Deficiency Categories - FY 98



Woolen, 1999

Investigator Responsibilities

- Failure to maintain records is considered non-compliance
- Failure to comply with the study protocol may:
  - Affects acceptability of trial data
  - Result in study termination
  - Suspension of research activities at the site
  - Result in fines

Steps in Drug Accountability

- Ordering
- Receiving
- Storage
- Dispensing
- Returning
- Transfers

Ordering

- Drugs must be ordered according to the study protocol
- The process may be vastly different between protocols, need to work with sponsor to determine how this is done
- Usually takes 2 – 4 working days to process orders
  - In urgent situations, may be able to process overnight

Receiving

- **Review shipping manifest and compare with actual drug delivered**
- **SAVE THE SHIPPING RECIEPT**
- **Sign in on Drug Accountability Record (DAR)**
  - * **Date received**
  - * **Strength and dosage form**
  - * **Quantity**
  - * **Manufacture and lot number**
  - * **Signature of person receiving**

Drug Accountability Record

- **Separate log for each protocol**
- **Part of regulatory documents**
- **Elements needed for DAR**
  - * **Protocol title and number**
  - * **Investigator**
  - * **Institution and dispensing area**
  - * **Drug name, form and strength**
  - * **Page number of DAR**
  - * **Balance**

Sample Drug Accountability Log

Form approved: OMB No. 0925-0240 Expires 11/30/2007

National Institutes of Health
National Cancer Institute

Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Investigational Agent Accountability Record

Name of Institution:
NCI Protocol No.:
Agent Name:
Dose Form and Strength:
Protocol Title:
Dispensing Area:
Investigator Name:
NCI Investigator No.:

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials
1								
2								
3								

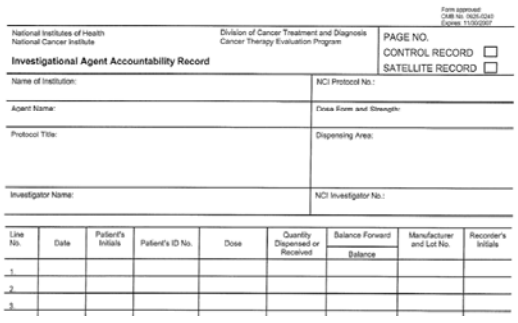
Storage

- Stored in labeled container with drug name, dosage and protocol
- Separate from commercial drugs
- Separate by protocol
- Separate by lot number
- Locked and limited access area
- Proper conditions
  * Temperature and humidity logs may be required

Dispensing

- Each transaction is recorded on the DAR
  * Date
  * Pt initials and ID number
  * Dose
  * Quantity
  * Manufacturer, Lot # and bottle number (if necessary)
  * New balance

Sample Drug Accountability Log



Form approved
OMB No. 0925-0240
Expires 11/30/2007

National Institutes of Health
National Cancer Institute

Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Investigational Agent Accountability Record

Name of Institution:
NCI Protocol No.:
Agent Name:
Dose Form and Strength:
Protocol Title:
Dispensing Area:
Investigator Name:
NCI Investigator No.:

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials
1								
2								
3								

Dispensing

- Drug that is prepared but not used must be documented as wasted
- Oral medications should be accompanied by a patient medication diary.
- The patient should bring back oral medication bottles for reconciliation
  - Even empty bottles
- Partial injectable vials
  - Some companies may want you to keep
  - Do not recommend doing this

Returns and Transfers

- Returns
  - Complete appropriate paperwork
  - Complete inventory balance
  - Drugs may be destroyed on site if authorized by the sponsor
- Transfers
  - May be transferred to satellite sites
  - Although not routinely done, study drug may be transferred between studies, if allowed by sponsor

Drug Accountability

A well designed system that accounts for drug from the initial shipment to final disposition and is error-free should allow for drug reconciliation in less than 20 minutes

References

- Friedman L. Managing drug accountability. Community Oncol. 2007:4;487- 9
- Lieck DJ, Bertram JE. Drug accountability at the investigative site. Applied Clin Trials. 2002:36-44.
- Woolen, SW. Improving Quality: What now. http://www.fda.gov/present/pediatric/phr99web. 1999. Accessed 2/18/2008.
- National Cancer Institute/Pharmaceutical Management Branch. Requisition and management of agents. http://ctep.cancer.gov/requisition/index.html. 2002. Accessed 2/18/2008

CONDUCTING CLINICAL TRIALS
Study Drug Accountability
STVHCS – Audie L. Murphy VAMC

Virginia Doyal, Pharm. D., BCPS

Points of Contact

Virginia Doyal, Pharm. D., BCPS
7400 Merton Minter Blvd.
Research Pharmacy (119)
STVHCS
San Antonio, Texas 78229
Telephone 210-617-5300 ext 16984
Fax 210-949-3820

Point of Contact

BMT Research Pharmacist
Michael John Gass, Pharm. D.
7400 Merton Minter Blvd.
STVHCS
San Antonio, Texas 78229
Telephone 210-617-5300 ext 16227 or 16597

Point of Contact

George Melnik, Pharm.D., BCPS
South Texas Veterans Health Care System
Clinical Pharmacy Coordinator
Pharmacy Research Coordinator
210-617-5300 ext 14463
210-949-3433 FAX

Research Accreditation

- VA Central Office mandates research accreditation
- NCQA -National Committee for Quality accreditation
- AAHRPP –Assurance Association for the Accreditation of Human Research Protection Programs – site visit September 2008
- Affiliate –UTHSCSA –IRB site visit Jan'09

The following documents per VA Policy Memorandum 119-05-05 should be present in the research pharmacy prior to delivery of an investigational drug to the research pharmacy and the initiation of dispensing of that drug:

1. Copy of protocol
2. Letter with R&D approval
3. Letter with IRB approval
4. VA 10-9012 (Invest Drug Information Record)
5. FDA 1572 or IND number (if appropriate)
6. Impact statement- signed by Chief of Pharmacy and Chief of Research Pharmacy
7. Invoice with documentation of drug delivery & source
8. Drug must have expiration date posted on label or invoice,or have a memo stating who will monitor that dating.

Prior to Dispensing study drug

- VA 10-9012 now needs to be scanned into the subject's electronic chart prior to dispensing study drug.
- Entire Signed Consent forms needs to be scanned into the subject's electronic record prior to dispensing study drug.
- Written/Electronic Order –prescriber listed on VA 10-9012
- List of authorized personnel who may pick up study medication from the research pharmacy for the patient
- Memo specifying the procedure for the research pharmacy for unblinding a subject;s study medication

Research Drug Storage outside Research Pharmacy

If investigational drug is stored outside the research pharmacy, a contractual agreement (approved by Chief of Pharmacy and Chief of Research Pharmacy) must be in completed prior to starting study.

- Please note: The storage of investigational drugs outside of the Pharmacy needs to be discouraged when a pharmacy is located within the VA facility per VA policies
- Example: TB Studies- DOT –Antibiotics stored in physician's office,

The Principal Investigator will maintain the investigational drug spreadsheet log containing the following information:

- Name of the drug
- Dosage form and strength
- Manufacturer or other source
- Date of receipt of the drug
- Quantity received
- Expiration date
- Control number
- Randomization number of the patient receiving the medication
- Name of investigator receiving medication, if applicable
- Quantity dispensed or transferred.
- Protocol number
- The amount of drug currently available
- Informed Consent is required for transfer medication.
- Transfer personnel will sign for the transfer shipment.
- A copy of Form 10-9012
- A final entry will be made when use of the investigational drug is discontinued. This entry will document the date of the termination of use the drug, the quantity remaining, and the action taken to dispose of the balance on hand.

Investigational Devices in Human Research

1. VA policy and procedures for the use of investigational devices in human research at the South Texas Veterans Health Care System (STVHCS) per FDA's IDE regulations, 21 CFR Part 812, other FDA regulations and VHA regulations.

2. The Department of Veterans Affairs (VA) clinical investigations of medical devices are subject to the Federal Food, Drug, and Cosmetic Act and unless exempted under certain specified conditions, are required to comply with IDE regulations as outlined in 21 CFR 812. VA investigators are expected to fulfill all of the responsibilities delineated in the Food and Drug Administration (FDA) regulations. The Pharmacy Service will document receipt, control, custody, and dispensing of the investigational devices.

The Principal Investigator is responsible for:

After obtaining approval for use of the investigational device by preparing and submitting appropriate documents for review to FDA and preparing a written protocol.

1. Protocol Approval by the Research and Development Committee and the Institutional Review Board. FDA approval must be obtained subsequent to IRB approval.
2. Delivering the investigational devices to the Pharmacy Service.
3. Ensuring the investigational devices are stored in a locked, secure area
4. Obtaining and properly documenting informed consent for the use of the device.
5. The consent and the VA 10-9012 (if applicable) will be electronically scanned into the subject's records with an enrollment note.
6. Maintaining records and accountability of all investigational devices.
7. Ensuring proper utilization of the investigational device as outlined in theapproved protocol.

The Research Pharmacy is responsible for:

(1) Receipt and storage— from the sponsor and will create an inventory of devices and accessories for the protocol.
(2) Accountability—An inventory log, with the lot number and expiration date of the investigational device and accessories, track the receipt and dispensing of investigational devices and accessories with invoices accompanying the shipment of the investigational devices and accessories.
(3) Dispensing—The investigational device and accessories will be dispensed to the protocol subject after a copy of consent form and the VA 10-9012 has been scanned into the subject's electronic record and upon receipt of an electronic order in CPRS or a written order signed by the principal investigator has been received.
(4) Disposal—Disposal of investigational devices and accessories after instruction is received from the protocol sponsor.

REFERENCE: M-2, Part VII, Chapter 6:

Compounding and Special Preparation Research Medications – Discussion and prior written approval agreement by Chief of Pharmacy and Chief of Research Pharmacy

- Compounding, making capsules, weighing powders/chemicals from canisters
- Special preparation procedures- defrosting, vortexer agitation, dilutions
- Manufacturing high risk sterile products
- Special Storage – refrigeration, - 70 degree centigrade freezer or large volume/amount dispensing.

- Fees – To be determined by Chief of Pharmacy and Chief of Research Pharmacy per agreement and impact statement.
- Covers receipt, storage and dispensing.
- Compounding & Preparation

Study Monitor Visits

The R&D Office must be notified of each study monitor visit and provided with a report of all findings.

Questions?

Adverse Events (UPIRSO)

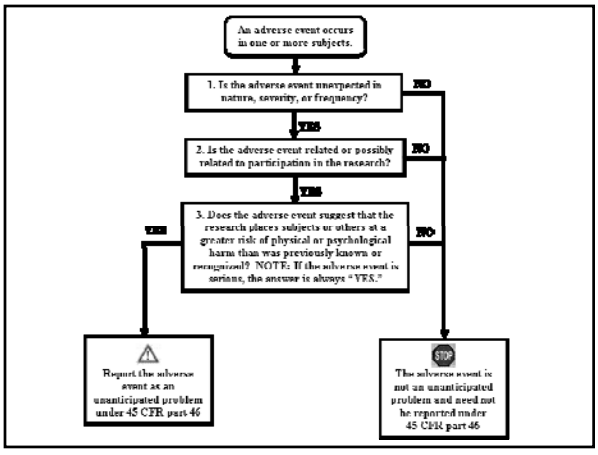
Roy Estrada, PhD, PA-C, CIP
Associate Director, IRB

Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO)

Roy R. Estrada, PhD, PA-C, CIP
Associate Director IRB
UTHSCSA

What?

- **The UTHSCSA Institutional Review Board (IRB) applies a reporting process based on federal guidance that may apply to any incident, experience, or outcome determined by the PI to be an unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)).**
- **The scope of what must be reported promptly to the IRB is narrow**



Other unanticipated problems not adverse events

- Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event; that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described [previously].

Scenario #1

- Ph II, clinical trial testing a new investigational antihypertensive drug, at UTHSCSA
- Determined by the IRB as greater than minimal risk
- No documented evidence of GERD associated with the drug
- 3 of 10 subjects had severe GERD that began within one week of starting drug
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE; Is it an AE?**
- **Report to IRB? If yes, what time frame?**

Categories of Reporting

- **Prompt reporting:**
  - **Promptly report all adverse events and unanticipated problems that might meet the definition of "Unanticipated Problems Involving Risks to Subjects or Others"**

Categories of Reporting

- **Prompt reporting:**
  - **Promptly report all adverse events and unanticipated problems that might meet the definition of "Unanticipated Problems Involving Risks to Subjects or Others"**
- **Non-Prompt Reporting:**
  - **Not meet definition of UPIRSO**
  - **Summarize Non-UPIRSO / UPIRSO in next progress report.**

Categories of Events

Adverse Events involve "physical or psychological harm"

Non-Adverse Event does not involve physical or psychological harm

Categories of UPIRSO Criteria

UNANTICIPATED e.g., not in the consent form, Sponsor Brochure, or labeling; not expected as part of subject's disease or condition

RELATED e.g., (or possibly related) a result of the research interaction/ identifiable data collection

GREATER RISK to subjects or others e.g., harm (including physical, psychological, economic, or social harm)

SERIOUS e.g., severe/life threatening/fatal

Categories of UPIRSO Criteria

UNANTICIPATED in Nature, Severity or Frequency

RELATED Reasonably Sure

GREATER RISK Greater Risk of harm than was previously known or recognized

SERIOUS relates to adverse events should always represent GR

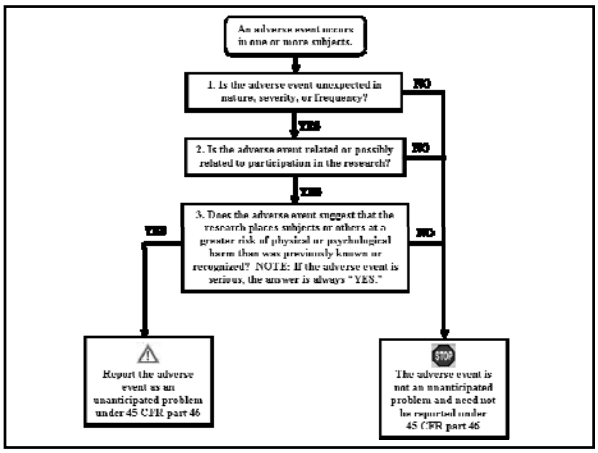
Scenario #1

- Ph II, clinical trial testing a new investigational antihypertensive drug, at UTHSCSA
- Determined by the IRB as greater than minimal risk
- No documented evidence of GERD associated with the drug
- 3 of 10 subjects had severe GERD that began within one week of starting drug
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External?**
- **Report to IRB? If yes, what time frame?**

Scenario #1 Is a UPIRSO

- **Internal Adverse Event**
- **Unanticipated and Related**
- **Not Serious**
- **Greater risk than previously known**

- **Prompt report**
- **Submit changes, submit UPIRSO report to IRB within 7 days**



Relatedness - Old Way

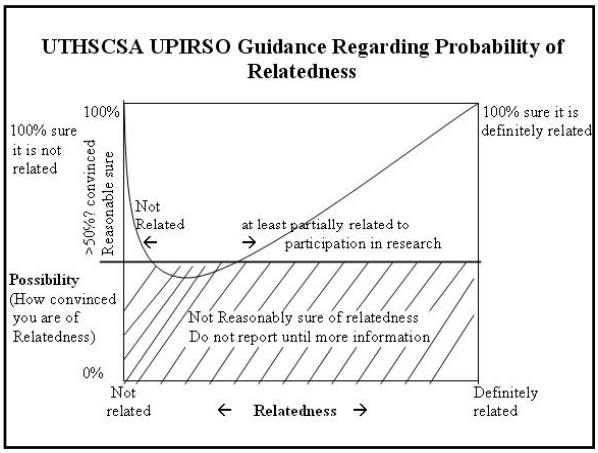
At least possibly related---→

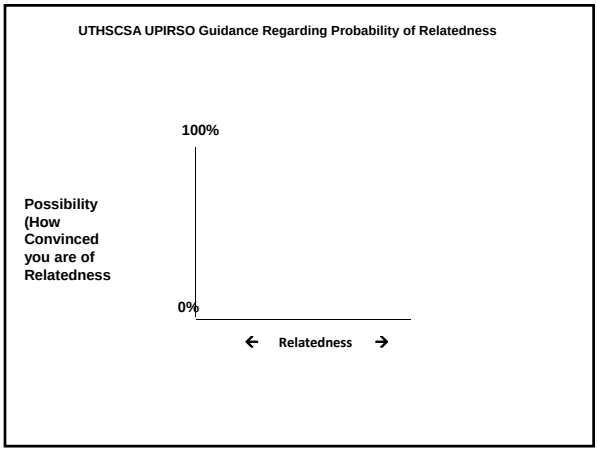
0% |----------| 100%

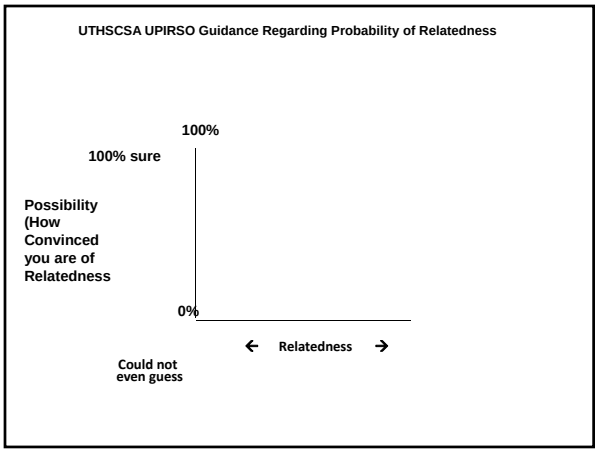
Not related — Definitely Related

Scenario #2

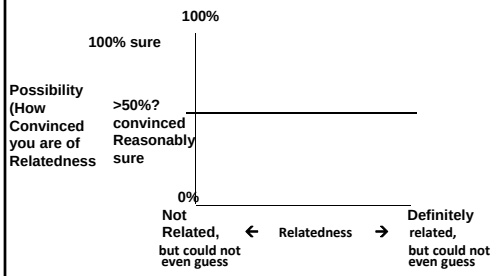
- International study -multiple countries-multiple sites
- UTHSCSA is IRB for local PI and VA PI
- Methods: interviewing 2000 mothers (mothers and babies are subjects) regarding breastfeeding (records)
- IRB determined to be minimal risk
- Known risks of breach of confidentiality
- VA study coordinator reports that 6 babies (subjects) died of malnutrition
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE?**
- **Report to IRB? If yes, what time frame?**


UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness
100%
100% sure it is not related
>50%? convinced Reasonable sure
100% sure it is definitely related
Not Related
at least partially related to participation in research
Possibility (How convinced you are of Relatedness)
Not Reasonably sure of relatedness
Do not report until more information
0%
Not related
Relatedness
Definitely related

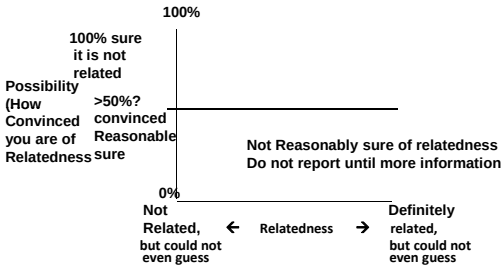

UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness
100%
Possibility (How Convinced you are of Relatedness
0%
Relatedness


UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness
100%
100% sure
Possibility (How Convinced you are of Relatedness
0%
Relatedness
Could not even guess

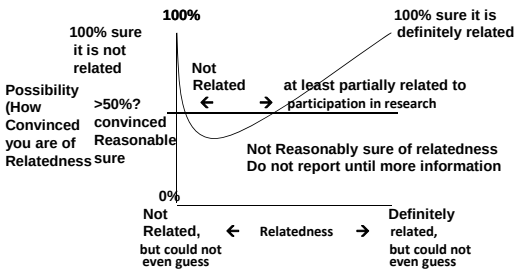
UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness



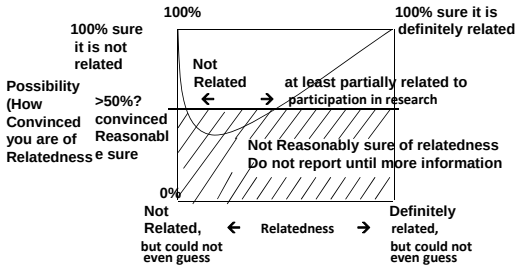
UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness



UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness



UTHSCSA UPIRSO Guidance Regarding Probability of Relatedness

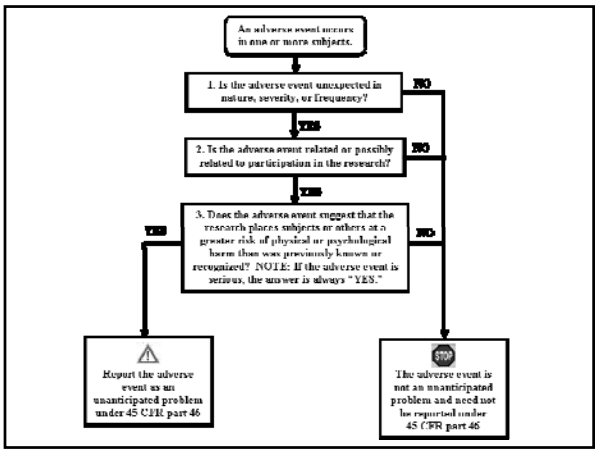


Scenario #2

- International study -multiple countries-multiple sites
- UTHSCSA is IRB for local PI and VA PI
- Methods: interviewing 2000 mothers (mothers and babies are subjects) regarding breastfeeding (records)
- IRB determined to be minimal risk
- Known risks of breach of confidentiality
- VA study coordinator reports that 6 babies (subjects) died of malnutrition
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE?**
- **Report to IRB? If yes, what time frame?**

Scenario #2 Is not a UPIRSO

- **Internal Adverse Event**
- **Unanticipated and Serious but Unrelated**
- **Prompt Reporting not required.**
- **Follow other reporting requirements listed in protocol (e.g., sponsored studies) as well**



Scenario #3

- Multi-center NCI study
- UTHSCSA one of 80 sites
- IRB determined - greater than minimal risk - DSMP
- Procedures include bone marrow transplant, chemotherapy, blood drawing, transfusions
- Risks listed in protocol documentation
- **Subject dies in Detroit site from complications of the chemo, UTHSCSA PI receives IND safety report**
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE?**
- **Report to IRB? If yes, what time frame?**

UPIRSO

UNANTICIPATED AND RELATED (possibly RELATED) events/problems that represent a GREATER RISK to subjects or others

Generally will warrant consideration of substantive changes

UNANTICIPATED and RELATED (possibly RELATED) and SERIOUS adverse events should also be considered to be represent GREATER RISK.

Always will warrant consideration of substantive changes

Examples of corrective actions or substantive changes

- Changes to eliminate apparent immediate hazards to subjects (before or after IRB approval);
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment;
- Suspension of research procedures;
- Modification of informed consent documents to include a description of newly recognized risks;
- Notification of previously enrolled subjects about newly recognized risks

Scenario #3

- Multi-center NCI study
- UTHSCSA one of 80 sites
- IRB determined - greater than minimal risk - DSMP
- Procedures include bone marrow transplant, chemotherapy, blood drawing, transfusions
- Risks listed in protocol documentation
- **Subject dies in Detroit site from complications of the chemo, UTHSCSA PI receives IND safety report**
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External?**
- **Report to IRB? If yes, what time frame?**

Scenario #3 Is not a UPIRSO

- **External Adverse Event**
- **Related, and Serious, and some argue Unanticipated vs. Anticipated**
- **If confusing**
  - **Substantive change required?**
    - **<u>Anticipated</u>**

Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document.

The investigators conclude that the subject's infection and death are directly related to the research interventions.

A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency.

Clarify at each level

ANTICIPATED in the consent form, Sponsor Brochure, or labeling; expected as part of subject's disease or condition

Can't Determine if RELATED when you are Not Reasonably sure

Represents a RISK but is it really a Greater Risk of harm than was previously known or recognized

Scenario #4

- UTHSCSA Ph II cancer trial on biologic made from human sera
- After 4 subjects enrolled audit revealed administered product was obtained from improperly screened donors (HIV,Hep-B risk)
- IRB determined it is greater than minimal risk
- Known risks: extensive
- No subject experienced any harm
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE; Is it an AE?**
- **Report to IRB? If yes, what time frame?**

UPIRSO

UNANTICIPATED AND RELATED (possibly RELATED) events/problems that represent a GREATER RISK to subjects or others

Only events that involve physical / psychological harm (AKA adverse events) can be SERIOUS

UNANTICIPATED and RELATED (possibly RELATED) and SERIOUS adverse events should also be considered to be represent GREATER RISK).

UPIRSO

UNANTICIPATED AND RELATED (possibly RELATED) events/problems that represent a GREATER RISK to subjects or others

Non-Adverse event

Only events that involve physical / psychological harm (AKA adverse events) can be SERIOUS

UNANTICIPATED and RELATED (possibly RELATED) and SERIOUS adverse events should also be considered to be represent GREATER RISK).

Adverse event

Scenario #4

- UTHSCSA Ph II cancer trial on biologic made from human sera
- After 4 subjects enrolled audit revealed administered product was obtained from improperly screened donors (HIV,Hep-B risk)
- IRB determined it is greater than minimal risk
- Known risks: extensive
- No subject experienced any harm
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE; Is it an AE?**
- **Report to IRB? If yes, what time frame?**

Scenario #4 Is a UPIRSO

- **Unanticipated and Related, although would not call it an *Adverse Event* and therefore "Seriousness" would not be determined as *no harm* occurred (physical or psychological harm).**
- **Greater risk**
- **Report to IRB promptly**

How Promptly?

- **Report all internal (<u>local</u>), unanticipated, related, life threatening or fatal events within 48 hours** (Submit only "Fatal toxicities" for NCI studies)
- **Report all others within**
  - **7 working days if based on internal information (e.g., internal AE) or**
  - **14 working days for all others**

How Promptly?

- **Internal Adverse Events**
  - **Adverse Events experienced by subjects enrolled by investigators approved by the UTHSCSA IRB to perform research at their respective institutions.**
- **External Adverse Events**
  - **Adverse Events experienced by subjects enrolled by investigators approved by IRB's other than UTHSCSA**

What about Deviations?

- **<u>Protocol Violations come in two flavors:</u>**
- **<u>Exceptions</u> are sought prior to implementation (Yes it deviates from the protocol but it is approved to do so by the IRB beforehand.)**
  - **Exceptions are not part of the UPIRSO process and are requested using an amendment form**
  - **For example a request for an exception to the inclusion criteria for a single potential subject**
- **<u>Deviations</u> are reported after they occur**
  - **Deviations are a measure of compliance**
  - **Deviations may also represent a UPIRSO**

How?

- Possible UPIRSO: AE or Non-AE UPIRSO Report
  - The report used for Prompt Reporting: Any incident, experience, outcome, Adverse Event or IND Safety Report, safety summary that constitutes a UPIRSO
- Non-Prompt Reporting
  - To report Any incident, experience, outcome, Adverse Event or IND Safety Report, safety summary that does not meet criteria for prompt reporting; Report in Progress Report.
- UTHSCSA Event Tracking Log - Optional
  - Assists you in summarizing on your next progress report: all non-prompt, non-UPIRSO and UPIRSO in relation to your entire study
- Forms can be found on our website http://research.uthscsa.edu/irb

How will reports be processed?

- Any Unanticipated Problem, or Adverse Event submitted is considered a possible UPIRSO and will be reviewed by an IRB Chair or designated reviewer.

Discovery process

- If Promptly Reported:
  - Possible UPIRSO Report will be reviewed by expedited or full IRB review as appropriate.
  - PI must act on requirements of involved institutions and requests for more information to resolve the issue.
  - PI must submit follow-up reports/report of resolution.

Determined to be a UPIRSO

- OIRB must report, PI must act:
  - ASAP report to involved institutions
  - Institutions will distribute internally
  - PI must gather requirements and act
  - PI must submit a follow-up report
    - "Is the action plan fully initiated and can we call the issue resolved"

UPIRSO Resolution

- IRB may act/IRB must report to OHRP:
  - Failing to meet deadlines for f/u reports may be considered noncompliance
  - IRB can suspend enrollment, suspend procedures or terminate a study
  - Suspensions, terminations and serious or continuing noncompliance are reported to OHRP
  - Final report to OHRP (± FDA)

How will reports be processed?

- If Prompt Reporting is not required:
  - The report will be returned to the PI with instructions to summarize in their next progress report
  - If sponsor required prompt reporting send them a copy of UTHSCSA policy letter.

Scenario #5

- UTHSCSA study of HIV patients
- Procedures include interviews, (e.g., illicit drugs)
- Known risk of loss of confidentiality but data is in password protected computer without encryption
- Event = computer with data is stolen
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE; Is it an AE?**
- **Report to IRB? If yes, what time frame?**

AE vs. Non-AE

- OHRP recognizes only a small subset of **adverse events** occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.
- Furthermore, there are **other types of incidents, experiences, and outcomes** that occur during the conduct of human subjects research that represent unanticipated problems but are **not considered adverse events**.
  - Examples: social or economic harm instead of the physical or psychological harm; increased *risk* of harm, but no harm occurs

AE vs. Non-AE

- OHRP recognizes only a small subset of **adverse events** occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.
- Furthermore, there are **other types of incidents, experiences, and outcomes** that occur during the conduct of human subjects research that represent unanticipated problems but are **not considered adverse events**.
  - Examples: social or economic harm instead of the physical or psychological harm; increased *risk* of harm, but no harm occurs

Adverse event

Non-Adverse event

Scenario #5

- UTHSCSA study of HIV patients
- Procedures include interviews, (e.g., illicit drugs)
- Known risk of loss of confidentiality but data is in password protected computer without encryption
- Event = computer with data is stolen
- **Anticipated or Unanticipated?**
- **Related or Unrelated?**
- **Serious? If not, Greater Risk?**
- **Internal or External AE; Is it an AE?**
- **Report to IRB? If yes, what time frame?**

Scenario #5 Is a UPIRSO

- **Local issue**
- **Unanticipated and Related and represents greater risk due to confidentiality of data**
- **Changes required?**
  - **Amend protocol to add improved security of data**
  - **Letter sent to those whose data was compromised.**
- **Submit UPIRSO report to IRB within 7 days**

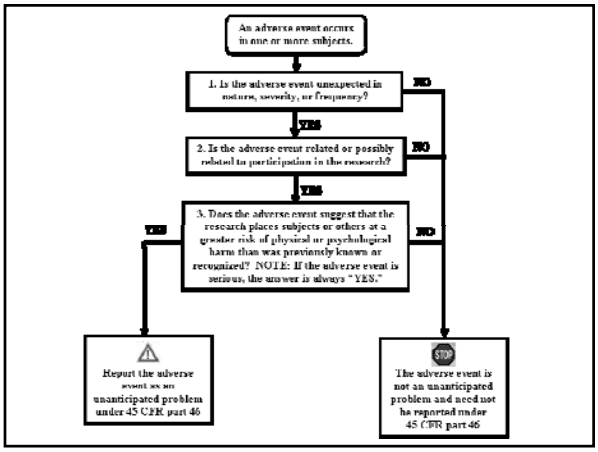
What if a change is needed?

➢**If an amendment is required:**

- **Submit ASAP.**
- **May qualify for expedite approval.**
  - **If minor change**
- **Substantive change**
  - **Amendment associated with UPIRSO will go to full IRB**
  - **PI must include thorough description of event and any immediate actions taken.**

What about accompanying documentation ?

- **Yes, with UPIRSO reports**
- **No, (e.g., IND Safety Reports) with progress reports**



Examples of corrective actions or substantive changes

- Changes to eliminate apparent immediate hazards to subjects (before or after IRB approval);
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment;
- Suspension of research procedures;
- Modification of informed consent documents to include a description of newly recognized risks;
- Notification of previously enrolled subjects about newly recognized risks

FDA

- Studies that require prior submission to the FDA require additional reporting to the IRB, the sponsor and the FDA
  - Unexpected drug experience (UDE)
  - Unexpected Adverse Device Experience (UADE)

UDE and UADE

- Unanticipated
  - only includes protocol documentation
- This is not necessarily a problem if you simply identify that you need to report to the sponsor the unexpected adverse drug experience and not report to the IRB since it is not a UPIRSO as it is not unanticipated by the condition of the subject (not outside frequency expected for their condition or predisposing risk factors).

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

- Defined by the FDA as any:
  - serious adverse effect on health or safety; **or**
  - any life-threatening problem; **or**
  - death
- **caused by, or associated** with, a device, **if** that effect, problem, or death was:
  - not previously identified in nature, severity, or degree of incidence in the investigational plan or **application** (including a supplementary plan or application), **or**
  - any other unanticipated serious problem associated with a device that relates to the **rights, safety, or welfare of subjects**.
-

UADE

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB (§ 812.150(a)(l))
  - as soon as possible,
  - but in no event later than 10 working days after the investigator first learns of the event.
- Sponsors must immediately conduct an evaluation of a UADE, and must report the results of the evaluation within 10 working days (812.46(b), 812.150(b)(l)) to:
  - All IRBs
  - All investigators
  - FDA

UADE

- So for devices you may find yourselves forwarding UADE's to the IRB but not as a UPIRSO and then later after investigation by the sponsor forwarding the results of the sponsors investigation as a UPIRSO if they discover that it is not as you suspected caused by the underlying condition but actually an effect of the device not previously known

QUESTIONS?

Roy R. Estrada, PhD, PA-C, CIP
Associate Director, IRB
UTHSCSA
(210) 567-3083
Fax (210) 567-2360
estradar3@uthscsa.edu