Good Research Practices (GRP)
Part 1
(Videotaped 10/14/2014)
Non-Clinical Research (Good Research Practices)

- 45 CFR 46

Overview of Good Research Practice (GRP)

- Historical Context
- Basic GRP Principles

GRP in Practice – Investigator Responsibilities

- Quality Assurance
- Delegated Activities
- Safety Reporting
- Informed Consent
- Documentation
Agenda – GRP Training (Cont.)

GRP Audit Readiness
- OHRP Inspection Process

Preventing Non-Compliance with GRP

Available Resources
Non-Clinical Research
(Good Research Practices)
The human subject protection requirements in the DHHS regulations provide requirements for good research practices for research, including research that is not clinical.

Good research practices include compliance with:

- Informed Consent Process
- Documentation of Informed Consent
- Data and Safety Monitoring
- Privacy
- Confidentiality
Good Research Practices Components

- Department of Health and Human Services (DHHS) regulations and guidance documents
- State and local laws
- Ethical Research Practice
- Medical Standard of Care
Shared Responsibilities

Responsibility for following GRPs is shared among the following:

- Institutional Review Board (IRB)
- Investigator
- Sponsor
- Monitor
Basic GRP Principles

1. Human Research should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with applicable regulatory requirement(s).

2. Before a study begins, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual subject and society. A study should begin and continue only if the anticipated benefits justify the risks.
Basic GRP Principles

3. The rights, safety, and well-being of the subjects are the most important considerations and should prevail over interests of science and society.

4. The research should be scientifically sound, and described in a clear, detailed protocol.

5. A study should be conducted in compliance with the IRB-approved protocol.

6. Any medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.
7. Each individual involved in conducting the study should be qualified by education, training, and experience to perform his or her respective task(s).

8. Freely given informed consent should be obtained from every subject prior to participation in the study.

9. All study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10. The confidentiality of records should be maintained, and the privacy interests of subjects should be respected.
Investigator Responsibilities (PHS & SUNY-B)

Investigator/Study Staff (PHS Regulations & SUNY-B P&Ps):

- Disclosure of Conflicts of Interest that affect the design, conduct, reporting, and analysis of the research (Disclose to Sponsor or granting agency and SUNY-B)
  - Compensation or equity interest of $5,000 or more
  - 5% or greater ownership interest
  - Executive position with sponsoring agency
  - Intellectual property interests
  - Compensation or equity interest of any amount that could be affected by the outcome of the research
GRP in Practice
**Follow** Approved Protocol

- Responsible for research team’s adherence as well

**Protect** Human Subjects

- Ensure informed consent
- Privacy and Confidentiality

**Document** Study Progress

- Submit appropriate reports
- Retain records (adequate case histories)
Investigator Responsibilities – Quality Assurance

GRP principles require investigators to ensure the following:

- Protocol procedures are followed
- Protocol deviations are documented and reported to IRB and sponsor
- Records and reports are accurate, complete, legible and timely
- Safety reporting is timely and as complete as possible
Delegate study-related activities only to qualified study team personnel

Determine study personnel are qualified by ensuring:

- Qualified by education, training and experience in the field being researched
- Maintains appropriate licensure for study-related duties that require a licensed professional
- Document that responsibilities are delegated only to qualified personnel
Investigator Responsibilities – Adequate Resources

Investigators must ensure the following resources exist prior to starting a research study:

- Sufficient access to the subject population being studied
- Sufficient time to properly conduct and complete the study
- Adequate number of qualified personnel
- Adequate facilities and equipment
- Personnel trained on protocol and assigned duties and functions
Investigator Responsibilities – IRB Review

Interaction with IRB:

- Written approval should be obtained for the protocol, informed consent form, advertisements, subject literature and amendments prior to being implemented.
- All documents to be reviewed should be provided in a timely manner and updated as necessary throughout the study.
Protocol Compliance:

- The investigator should not deviate from the protocol without prior knowledge and agreement from the IRB.
- The investigator should not implement protocol amendments prior to review and approval by the IRB.
Data and Safety Monitoring Plans

Protocols that are greater than minimal risk require a data and safety monitoring plan.

This plan should outline how you will monitor:

- Individual subject safety
- The conduct of the research
- The data collected

The plan should also tell us:

- Who will review the data
- What data will be reviewed
- When and how often the data will be reviewed
Informed Consent

• Documented approval of the consent document by IRB
• Revisions to consent document approved by IRB and subjects notified of changes when appropriate
• No subject should be coerced or unduly influenced to participate or continue to participate in a research study
• No exculpatory language that causes the subject or the subject's legally authorized representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence
Informed Consent

• Investigator, or designee, should fully inform the subject, or the subject's legally authorized representative, of all pertinent aspects of the study

• Written informed consent form, should be understandable to the subject or the subject's legally authorized representative

• Provide the subject, or the subject's legally authorized representative, ample time and opportunity to decide whether or not to participate in the study
Informed Consent

• Written informed consent form should be signed by the subject, or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion.

• If a subject, or legally authorized representative is unable to read, an impartial witness should be present during the informed consent discussion, and sign the consent form attesting that the information in the consent form was accurately explained to, and apparently understood by, the subject or the subject's legally authorized representative.
Informed Consent – Required Elements

- Study involves research
- Purpose of study
- Study procedures
- Investigational procedures
- Risks/inconveniences
- Expected benefits
- Alternatives
- Compensation for injury
- Prorated payment
- Expenses
- Voluntary, free to withdraw
- Direct access to records
- Confidentiality
- New information timely
- Contact person
- Duration
- Number of subjects
Informed Consent

• Subject, or subject's legally authorized representative should receive a copy of the written informed consent form.

• Subjects who can only be enrolled in a study with the consent of a legally authorized representative should be informed about the study to the extent compatible with the subject’s understanding and, if capable, the subject should assent and sign the written informed consent.
Informed Consent

• Studies with no anticipated benefit should be conducted only on subjects who personally give consent and who sign the written informed consent form (with specific exceptions)
  o Objectives of the study cannot be met by involvement of only subjects who can give informed consent personally
  o The foreseeable risks to the subjects are low
  o Negative impact on the subject’s well-being is minimized and low
  o Approval of the IRB is expressly sought on the inclusion of such subjects
Documentation Requirements

• Accurate, complete, legible, and timeliness of data and reports reported to sponsor or granting agency and IRB
• Financial aspects of the trial should be documented in an agreement between sponsor or granting agency and investigator/institution
• Upon request of monitor, auditor, IRB, or regulatory authority, investigator should make available for direct access all requested trial-related records
GRP Audit Readiness
OHRP Inspection Process

• OHRP sends inquiry letter to institution describing allegations of non-compliance or regulatory violations
  o Asks institution to conduct an internal investigation
  o Asks for a written response following investigation by specified date with supporting documentation
  o Submission of corrective action plan, if applicable
  o PI receives copy of inquiry letter

• OHRP evaluates the response and determines whether there is non-compliance with HHS regulations
  o If non-compliance is found – a Determination Letter is issued.
OHRP Inspection Process

• Determination Letter includes:
  o Specific indications of non-compliance
  o Proposed corrective action and the extent to which this plan adequately addresses the issues of non-compliance
  o If no corrective action plan previously submitted, OHRP will designate a date by which one must be submitted
    ▪ OHRP will make recommendations or will assist in development of corrective action plans.
  o If corrective action adequately resolves the non-compliance, the case is closed
  o If not, OHRP will conduct a for-cause compliance oversight evaluation
OHRP Inspection Process

- Outcomes of for-cause compliance oversight evaluation:
  - No non-compliance found
  - OHRP recommends specific improvements (voluntary)
  - OHRP determines non-compliance with HHS regulations
    - OHRP requires specific corrective action
  - OHRP may restrict or attach conditions to the institution’s FWA, such as:
    - Requiring special reporting (quarterly) to OHRP
    - Requiring education and training (HSP or GCP)
OHRP Inspection Process

• Outcomes of for-cause compliance oversight evaluation:
  o OHRP may:
    ▪ Suspend its approval of the Institution’s FWA
      ❑ All research under the purview of OHRP will be suspended until the FWA is re-instated
      ❑ If this occurs, any other research conducted by another federal agency that relies on the DHHS FWA (e.g., FDA) must be suspended until the FWA is re-instated
    ▪ Suspend the conduct of a specific research protocol until specified protections or corrective action has been
      ❑ OHRP will consider whether it is in the best interest of subjects to continue on the study during this suspension.
    ▪ Temporarily or permanently remove the institution or an investigator from participation in specific research projects
    ▪ Notify HHS scientific peer review groups (e.g., NIH) of an institution’s or investigator’s previous non-compliance prior to review of new projects.
    ▪ Debar an institution or investigator
OHRP is Coming – Now What?

- Will give you a timeframe for audit
- Gather all study and source documentation
- Alert study staff
- Assign and define inspection roles
  - Host
  - Interviewee
  - Scribe
  - Runner
  - Escort
OHRP is Coming – Now What? (cont.)

• Discuss ground rules with study staff on answering questions, be honest and truthful, etc.

• Find a workspace for the auditor(s)
  o Out of earshot
  o Comfortable
  o Provide a desk

• Document what you provide to the auditor(s)

• Check what the auditor(s) returns
OHRP is Coming – Now What? (cont.)

• OK to ask
  o Questions
  o An explanation of the regulatory basis

• Recommended actions
  o Take responsibility (Don’t blame others)
  o Be careful about offering unrequested information
Generally Not Persuasive to Regulators

- Not responding to audit findings (Determination Letters)
- Vague or general responses to audit findings
- Blaming 3rd parties for deficiencies
- Asserting that another regulatory authority or sponsor/funding agency had different findings
- Absence or loss of records (due to hurricanes, floods, fires, etc.)
Negative Implications of an OHRP Audit

- Site shutdown
- PI Disqualification
- Bad publicity
- Legal Issues
Points To Consider When Responding to Audit Findings

• Take findings SERIOUSLY
• Accept responsibility as appropriate
• If the audit findings are inaccurate, explain why and provide specific documentation to support the explanation
• Indicate a clear understanding of the scope and root cause of the problem
Points To Consider When Responding to Audit Findings

• Propose corrective action plan that addresses current and future studies
  o Consider whether SOPs need revision, need for periodic training
  o Offer item-specific responses, strategies to correct specific problems

• Feel free to contact for clarification, questions, and suggestions
Be Prepared for Audits

• Have all study materials available in one place
• Print out electronically stored records, or provide on-site access for auditor
• Do not make any “after the fact” changes or revisions to study documents
• Provide adequate space for auditor
Written Materials to Ensure Appropriate Supervision and Conduct

• Job descriptions, training plans, on-the-job training documentation, training records, licenses, CV and resume
• PI supervision, oversight, delegation, staff qualifications for study responsibilities
• Procedural documents (SOPs, forms etc.)
  o Make sure you follow your SOPs
Most Common Findings in OHRP Determination Letters

- Research conducted without IRB review/approval
- Failure to report unanticipated problems, Non-compliance, suspensions and terminations to the IRB, IO, OHRP
- Changes in research initiated without IRB review/approval
- Failure to obtain legally effective informed consent
- Failure to document informed consent
- Failure to provide copy of consent document to subjects
Common Audit Findings

- **Informed Consent**
  - Missing or incomplete
  - Incorrect version used
  - Re-consenting not done
  - Incorrect language
  - Process not documented

- **Regulatory**
  - AEs, protocol deviations/violations not reported
  - Inadequate supervision and oversight
  - Lapse of approval

- **Staff Qualifications**
  - Improper delegation of duties
  - Study personnel not properly trained on protocol

- **Protocol Compliance**
  - Study procedures not performed
  - Lack of database

- **Documentation**
  - No study logs
  - Lack of source documentation
Preventing Non-Compliance with GRP
Ensure High Quality Data and Subject Safety

Build quality into the conduct of the study

- Create systems that limit opportunity for errors
- Simplify protocol and outcomes assessments
- Standardize systems and formats where possible, use validated instruments/definitions
- Keep protocol amendments to a minimum and check consent forms against each change
- Insist on training (protocol-specific and HSP)
- Have a disaster plan, e.g. back ups if key study staff leave or site experiences flood or disaster
- QA/QI
Adequate Training

Ensure that staff:

- Have a general familiarity with the study and the protocol
- Have a specific understanding of the details of the protocol relevant to the tasks they will be performing
- Are aware of regulatory requirements and acceptable standards for the conduct of human subject research, both in respect to conduct of the study and human subject protection
- Are competent to perform the tasks that they are delegated
- Are informed of any pertinent changes during the conduct of the study and educated or given additional training as appropriate
Adequate Supervision

• Routine meetings with staff to review study progress and update staff on any changes to the protocol or other procedures
• Written materials to ensure appropriate supervision and conduct
A common cause of errors in research is staff who are unwilling or unable to raise issues due to the perceived or actual authority of the investigator.

Solutions:

- Listen to your staff
- Encourage staff to raise concerns
- Work as a team
Available Resources
Resources

HRP-103 – Investigator Manual
HRP-503 – Template Protocol
HRP-502 – Template Consent Document
Informed Consent SOPs
  • HRP-090 – SOP – Informed Consent Process
  • HRP-091 – SOP – Documentation of Informed Consent
HRP-430 – Checklist – Investigator Quality Improvement Assessment

DHHS  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
Clients include:

- More than 95 of the top 100 research universities
- Nine of the top ten largest healthcare systems
  - ranked by Modern Healthcare
- Eight of the top ten largest Children’s hospitals
- Many of the premier academic medical centers