Non-Compliance

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The Principal Investigator (PI) is the individual who has full and final responsibility for the conduct of the research.
PI Responsibilities

- Adequate resources
- Adequate training of staff
  - Individuals should be trained on the duties delegated by the PI
    - CV, special certification
    - Documentation (sign in sheet) that the PI conducted a training session where the study team was trained on the protocol
- Maintain all approved study documents in the study file

PI Responsibilities

- Maintain all approved pages of the signed consent form
- Timely submission of reports to IRB
  - Continuing Review
  - Reportable Events
  - Closure - Submit a final progress report to the IRB upon completion of this study
PI Responsibilities

• Amendments - obtain IRB approval for any proposed change in research *before* implementing the change
  – All subject recruitment materials must be approved prior to use
  – Changes may not be initiated without IRB approval except when necessary to eliminate apparent immediate harm to subjects and then a report must be submitted along with the amendment request

PI Responsibilities

• Protocol Compliance
  – DO NOT DEVIATE from the protocol unless necessary to eliminate immediate harm to subjects
    • Must be reported after the event occurred
    • Document and explain any deviation
  – Report deviations that may affect subject safety *immediately* to the IRB
    • Dosing errors, failure to perform a safety measure, loss of identifiable data (stolen laptop)
What is Non-Compliance?

• the act or state of not complying to a desire, demand, proposal, or regimen
• the failure or refusal to follow rules, regulations, or the advice or wishes of another.
  – In medicine, commonly used to refer to a patient who does not take a prescribed medication or follow a prescribed course of treatment

What is Research Non-Compliance?

• RSRB definition
  – Failure to follow the federal regulations or state laws for the protection of human subjects in research or
  – failure to follow the requirements or determinations of the RSRB with respect to the conduct of research as approved by the RSRB
Types of Research Non-Compliance

- **Minor**: Non-compliance that does not result in an increased risk to subjects or others.
- **Sporadic**: Non-compliance that does not indicate a pattern and does not result in increased risk to subjects.
- **Serious**: Non-compliance that results in an increased risk to subjects or others.
- **Continuing**: A pattern of non-compliance that continues despite identification by the RSRB, notice to the investigator, or prior submission of a corrective action plan. This pattern may or may not result in increased risk to subjects. Although it may be due to a variety of factors, continuing non-compliance implies that an investigator is either unwilling or unable to develop and apply successful corrective measures.

Minor Non-compliance

- **Minor** - may involve records or a procedure that while not correct, it will not adversely affect the validity of consent or the safety of subjects, possible examples include:
  - Using expired consent or recruitment forms…same content
  - Using consent form without the RSRB watermark or without the first page on letterhead
  - Not maintaining a complete copy of the signed consent form in the study records
  - Study personnel conducting research who are not listed as research personnel in study application, but have training in human subject protection (EPRP or HSPP)
  - Over enrollment
Serious Non-compliance

- **Serious** - Exposed subjects to risk unnecessarily, possible examples include:
  - Conducting research without RSRB approval or revising the protocol without RSRB approval
  - Enrolling subjects who were not eligible
  - Not performing safety measures
  - Failure to obtain consent from a research subject

An RSRB determination of serious non-compliance requires reporting to the institutional officials (Sr. VP for Research, Department Chair, legal), federal regulators (OHRP, FDA) and Study Sponsors (NIH, foundation).

Minor Vs. Serious Examples

- Performing procedures not identified in the approved study protocol
  - What was the procedure….extra EKG vs. biopsy?
- Enrolling subjects outside of the eligibility criteria
  - Two years out of age range older vs. enrolling healthy controls without approval
- Lapse in approval
  - All research stopped or research was conducted

*Disclaimer…the full board will always make the final determination regarding Serious Non-compliance.*
Sporadic Non-compliance

• **Sporadic**: Random occurrences of minor non-compliance, no consistent pattern. Possible example:
  - PI used a consent form that was not watermarked to consent one subject in one study, but it was the correct version.
  - A year later, the same PI has lapse in RSRB approval.

Continuing Non-compliance

• **Continuing**: Initial incident with board determined corrective/preventive action plan and then another incident of non-compliance occurs. Increased risk is not required. An example:
  - Continuing issues with appropriately documenting consent and/or renewing RSRB approvals in a timely manner
  - Board reviews incident and approves a corrective/preventative action plan
  - The PI continues to fail to document consent appropriately and/or renew RSRB applications prior to expiration
  - Incident returns to the board for review and determination

**An RSRB determination of continuing non-compliance requires reporting to the institutional officials (Sr. VP for Research, Department Chair, legal), federal regulators (OHRP, FDA) and Study Sponsors (NIH, foundation).**
Reports or Allegations of Non-compliance

- **Continuing review:** The RSRB may learn of potential non-compliance through its continuing review of ongoing research.
  - Date first subject was enrolled
  - Accrual numbers
  - Review of the last signed consent form(s)

- **Information identified during the review of an amendment**

- **Direct report to the RSRB by an individual or an organization**

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Reports or Allegations of Non-compliance

- **Audit by OHSP:** the OHSP conducts routine and for-cause audits of research studies approved by the RSRB. These audit reports may reveal area(s) of non-compliance.

- **Report through the Medical Center Office of Compliance:**
  - Compliance Office investigation
  - Hot line
Process for Review

Each allegation of non-compliance is evaluated to determine validity.

Inquiry Phase

– RSRB Staff/Board Chair collects information from the study team and PI and may collect copies of study documents, etc.

– Information is reviewed by the Board Chair
  • No basis, explanation addresses concern
  • Merit, but non-compliance is not serious or continuing, corrective/preventative action developed.
  • Merit and possibility that the non-compliance is serious or continuing…referred to the board.
  • If the Board Chair is concerned about subject safety, he/she may suspend further research activity…requires reporting to the institutional officials, Federal regulators and Study Sponsors.

Process for Review

Board Review Phase

– Board members review all written materials related to the allegation of non-compliance

– Result
  • Minor or sporadic non-compliance…review action plan and make changes or accept
  • If the board feels it may be serious or continuing non-compliance…vote to “open an investigation into serious/continuing non-compliance”
    – Request additional information, further OHSP auditing, etc.
  • If the board is concerned about subject safety, board members may vote to suspend further research activity … requires reporting to the institutional officials, Federal regulators and Study Sponsors.
Process for Review

Investigation into Serious/Continuing Noncompliance

- Principal Investigator receives written notification that investigation has been opened (copy to institutional officials, legal)
- Board’s request for additional information are completed
- Legal consultation
- When all information related to the investigation is compiled, all materials are sent back to the convened board for review and consideration
- Final determination regarding serious/continuing noncompliance is made by the full board at a convened meeting.
- Principal Investigator receives written notification of the results of the investigation (copy to institutional officials, legal)

If SERIOUS or CONTINUING, formal letter prepared by the RSRB Director to notify institutional officials, Federal regulators and Study Sponsors of finding.

Possible actions of the board

- Dismissal of the allegation
- No action (e.g., for minor, sporadic, closed studies, etc.)
- Cautionary reminder
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to former subjects
- Notification of current subjects (when such information may relate to their willingness to continue to take part in the research)
- Requiring subjects to renew consent to participation or to post hoc data use
- Modification of the continuing review schedule
- Monitoring of the research
- Monitoring of the consent
- Remedial education of the investigator
- Restriction of data use/publication
- Restriction of investigator’s research approvals
- Suspension of the research approval
- Termination of the research approval
- Referral to other organizational entities (e.g., OHSP, University Audit, UR Office of Counsel)
Investigator Voluntary Suspension

- An investigator has the ability to voluntarily suspend a portion or all research activity at any time, if the investigator thinks it would be appropriate.
  - A serious issue, which may or may not involve subject safety, is identified that requires further investigation and training to correct or prevent the issues from occurring in the future.
    - Safety measures not being performed
    - Not collecting adverse events
    - Serious consent form issues
- A voluntary suspension by an investigator does not trigger automatic reporting outside of the institution.

Action Plans

- Corrective Action Plan - Correct what has been done
  - Reconsent
  - Provide additional information to subject
- Preventative Action Plan – Prevent what occurred from happening in the future
  - System to ensure the correct version of the consent form is used
  - System to ensure that new study personnel have human subject protection training and are added to the RSRB application before participating in the research
  - Education & Training
  - Mentoring
  - Study Team Meetings
Findings of Non-Compliance

• It is not the intent, nor the scope, of the RSRB to punish investigators
• However, a finding of noncompliance does have consequences.
• Noncompliance that raises academic discipline issues (e.g., scientific misconduct) will be referred to the proper University channels for investigation.

Mistakes happen….what do I do?

• Call your RSRB Specialist
• Possible Fixes
  – Note to File…Reporting still required
  – Re-consent
    - Current version of the document
    - Person obtaining consent does not have to be the one to re-consent
    - Use current date
  – Exclude data
• Reporting
  – Reportable Event via ROSS as non-compliance (type 8);
  – Question 5.8 on Progress Report
Questions