The Importance of Protocol Adherence: Why it Sometimes Doesn't Happen and How to Ensure It Does!

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Learning Objectives

- Explain the importance of protocol adherence in overall quality of the research
- Describe examples of non-compliance to the protocol and effects on research participant safety as well as data quality
- Review what to do in the case of a deviation(s) to the protocol
- List specific elements that help to ensure protocol adherence

Synopsis

Following an IRB-approved protocol is imperative for the safety of human subjects as well as the quality of the data to answer the study question. It may seem a simple thing: what we have to do is right there, in writing! However, non-compliance related to protocol adherence is one of the top three major-deviation findings by the OHRA Research Quality Program Quality Assurance reviews (and FDA inspections). In actual practice, following the protocol is not as simple as we would hope. Join us for this seminar as we delve into what it means to follow the protocol, reasons why the protocol isn't followed, best practices for following the protocol to ensure the highest quality in our conduct of the research, protection of our study participants, and in the end getting the best data possible to answer the study questions.

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What do I mean when I say Protocol?

- Protocol Document detailing the research Background, Purpose, Objectives, Design/Methodology, Procedures, Analysis, Safety Monitoring, Ethical standards, etc.

Also includes:

- IRB application
- Participant-facing materials such as recruitment materials, instructions, scripts, etc.
- Consent form(s)
- Data Safety Monitoring Plan (if separate from protocol document)

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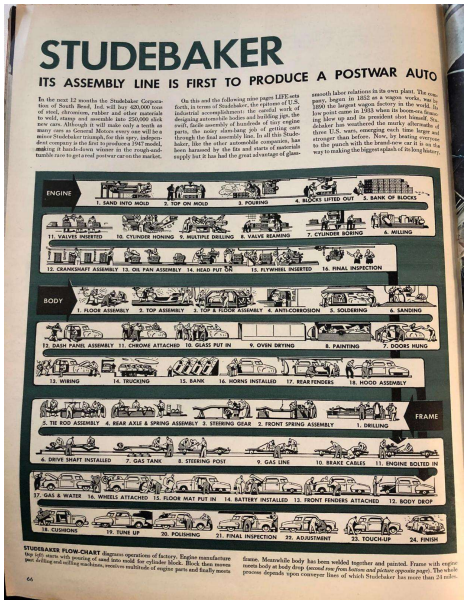
Why is Protocol Adherence Important?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Will this product work the way it's supposed to?

Will this product be safe?

Can I trust this product?

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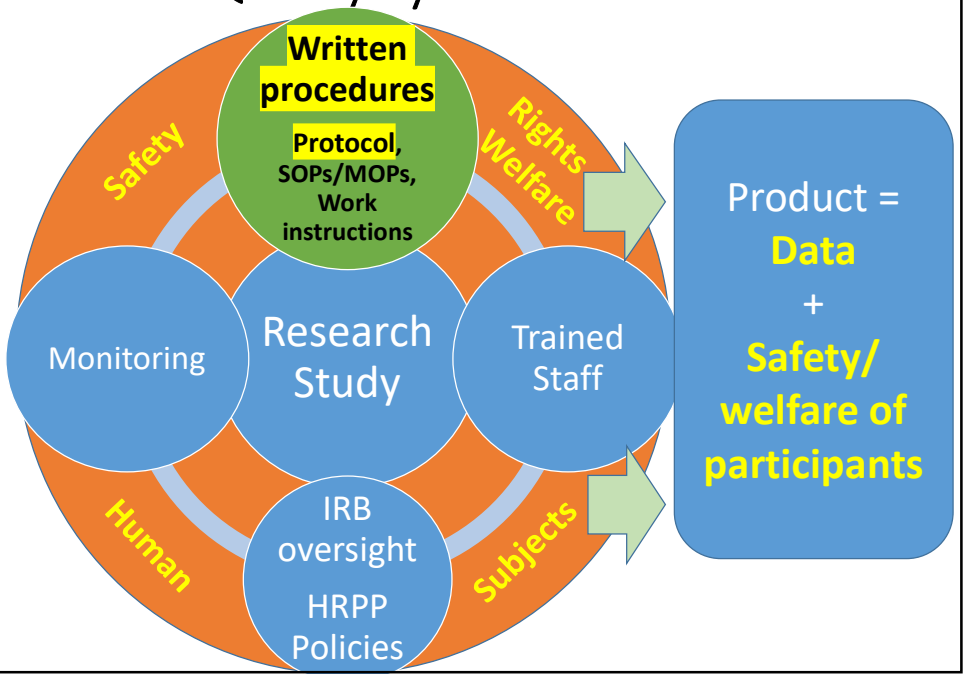
Clinical Research as a Quality System

Documents the policies, procedures, and controls necessary for an organization to create and deliver high-quality products or services.

GOALs:
Ensure consistency; reproducibility



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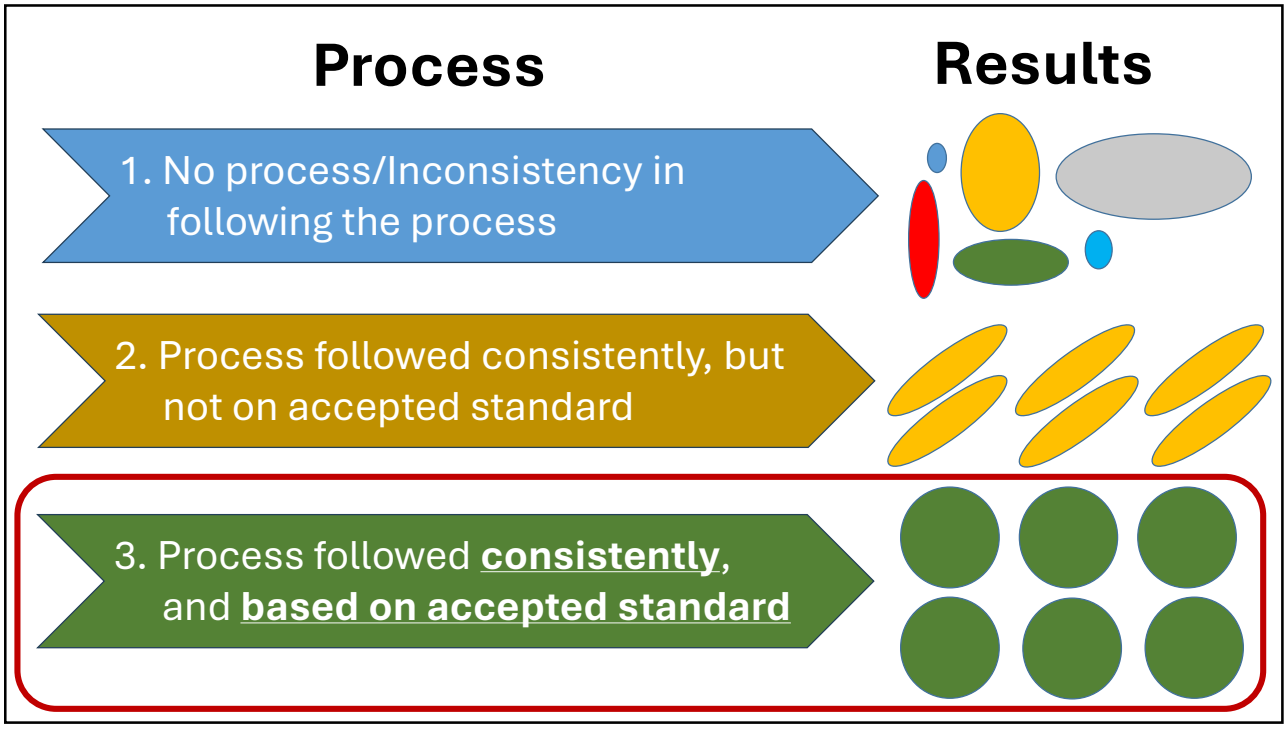

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Is not following the protocol a big problem?

- **FDA Inspections:** #1 finding is failure to follow the investigational plan
- **OHRA Research Quality Program (RQP) QA Reviews:** #1 deviation is not adhering to the protocol/research plan

- OHRA RQP program metrics data from 2017 – 2025:
  - On average, each QA review results in just over 1.5 deviations related to protocol adherence (areas of informed consent, eligibility/screening, post-enrollment protocol adherence, safety monitoring)

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What are Consequences of Non-Adherence?

- Increased risk to participant
- Actual harm to participants
- Breach of our ethical obligations to participants
- Data that is incomplete, not reliable
- Data cannot/should not be included in the analysis
- Rejection of data (FDA); studies must be redone
- Harm to future patients if unreliable data is used to answer the questions
- LOTS of time spent by study team (and others) to correct the problems
- Possible future audits of the study
- Possible regulatory actions (FDA and/or OHRP)

Erosion of public trust in the research enterprise

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FDA Warning letter excerpt

(*Lightner, March 25, 2025)*

You failed to ensure that an investigation was conducted according to the signed investigator statement, the investigational plan, and applicable regulations. 21 CFR § 312.60.

- The protocols for studies **(b)(4)** provide for exclusion of subjects based on specific criteria, including tests for **(b)(4)** panels. These protocols also specified procedures for recording and reporting Adverse Events (AEs).
- As a Sponsor-Investigator you failed to adhere to requirements specified in protocols **(b)(4)** for determining if subjects met specified eligibility criteria to be enrolled in the relevant clinical investigation. For example:
- The following subjects were dosed with the IP prior to collecting samples and obtaining the results of eligibility screening tests that are required by the protocol prior to enrolling subjects in the studies listed and to adequately evaluate subjects for exclusion from the study…

****

- **We emphasize that as a sponsor-investigator, it is your responsibility to ensure that your clinical investigations are conducted in compliance with the FD&C Act, PHS Act, and applicable FDA regulations, both to protect the rights, safety, and welfare of subjects, and to ensure the integrity of study data.**

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Dr. Jane Henney, Commissioner, FDA, May 11, 2000
In response to tragic death of research participant Jessie Gelsinger

"What we have witnessed – esoteric or complex standards have not been the issue, but rather the most basic elements of what it takes to properly conduct clinical studies…

- Enrollment of patients who did not meet the eligibility criteria for the study;
- Failure to report adverse events as required;
- Failure to ensure that a protocol was followed;
- Inadequate training for study staff;
- Investigators changing protocols without proper notice to the IRB and to FDA;
- Failure to incorporate agreed-upon protocol changes…"

"…I would underscore, these are not isolated incidents occurring on the fringes of science or by physicians with no academic credentials. We have found these problems in some of the most renowned research centers in the country and these unacceptable practices by leaders in their fields of study."

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Protocol Adherence
What does ICH GCP (R3) say?

- **2.5 Compliance with Protocol**
  - 2.5.2 The investigator should comply with the protocol, GCP and applicable regulatory requirements *(Note: 2.5.3 Coming in a few slides)*
  - 2.5.4 The investigator should follow the protocol and deviate only where necessary to eliminate an immediate hazard(s) to trial participants. In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor promptly.

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Protocol Adherence and FDA Regs

General Responsibilities of Investigators (21 CFR 312.60)

- An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, welfare of subjects under the investigator's care…

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Protocol Adherence and HRPP Policies

General Responsibilities of the Principal Investigator (HRPP Policy 6.6.1)

6. Ensure that prior to beginning work on the study, the Principal Investigator and all members of the research team …. have all required training, qualifications, credentials, and licenses; and are trained on and appropriately delegated responsibility for study procedures

7. Not initiate any human subjects research activities until an IRB final outcome letter has been received and all required institutional approvals have been obtained

8. Be responsible for execution and management of the study, including oversight of all study personnel …

9. Comply with all applicable terms, conditions, assurances and certifications referenced in the application, award (grant or contract), and protocol ….

10. Follow the IRB-approved research plan by ….

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What are some reasons why it's important to follow the IRB-approved protocol/research plan?

(Responses are anonymous; you can submit multiple responses.)

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Importance of the Protocol

- Participant Safety and Welfare
- Ethical Compliance
- Scientific Integrity and Validity
- Regulatory requirements
- Trust and Accountability

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Changes to the Protocol

- All changes to study protocol must be:
  - **Submitted to the IRB**, and
  - **Approved by the IRB <u>prior to being initiated</u>**

- **Only exception: <u>a change that eliminates immediate hazards</u>**
- This can be initiated without prior IRB review and approval, <u>however</u>…

Report to IRB ASAP

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Prospective changes to the Protocol: Amendments & Exceptions

- **Protocol Amendment:**
  - Submission to the IRB, making a prospective change to the *overall* protocol
- **Protocol Exception:**
  - Submission to the IRB, requesting a one-time change to the protocol prospectively without actually altering the overall protocol
  - This should be rare as the protocol should already have flexibility built in (where it makes sense)
    - Note that per FDA (but not our HRPP) this is technically still a deviation from the approved protocol. It is acceptable as it has gone through review to assess impacts on data and participant safety.

Important! For amendments and exceptions:

- Must get approval from the IRB *and* Sponsor/lead site if applicable
- If the investigator is holding the IND or IDE (i.e. sponsor-investigator) then FDA must be notified through a protocol amendment
  - Change can be implemented once submitted to FDA, as long as IRB approved the change
- Make sure to keep documentation of approvals

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Changes to Exempt research

- Staff additions must be submitted to IRB and approved prior to beginning work on the study
- Changes to research plan are permitted without IRB submission as long as the change doesn't alter IRB determinations
- Common reasons to submit amendment for exempt research:
  - Change in protections for privacy and confidentiality; or
  - Change in funding; or
  - Change in recruitment procedures; or
  - Change in information provided for a waiver of authorization for use and disclosure of Protected Health Information; or
  - Change in procedures related to the retention of data or samples for extra use

See: HRPP P&Ps 10.2.5.1

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Protocol Amendments when relying on an external IRB: What must still be submitted to the local IRB (i.e. BMC/BUMC IRB)?

- If changes affect compliance with local policies or seek to modify previously-granted exception requests for enrollment of:
  - Decisionally impaired subjects w/an LAR
  - Non-English speaking subjects
  - Wards of the state
  - Limited and non readers
  - Students, trainees, employees
  - Patients of Substance Use Disorder clinics
- If change affects compliance with local policies or seeks to modify previously granted policy exception requests for enrollment
- Affect info provided regarding the plan to prevent disclosure of HIV testing status to non-BMC research staff before written consent
- Affect info provided on plan to share data with 3rd party vendor
- Affect info provided regarding recruitment or modification of recruitment materials
- Affect info provide for waiver of authorization for use and disclosure of PHI
- Require review by a special routing individual or entity not involved in initial review
- Add new or modify existing investigator or research staff FCOI
- Affect info provided regarding organizational COI
- Adding new study cohorts and/or new ICFs

See HRPP Policies 10.2.3.1.2

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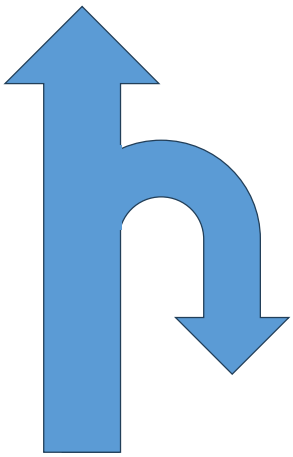

Protocol Deviation

"Any change, divergence, or departure from the study design or procedures defined in the protocol."

(FDA definition)

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Deviations from the IRB-approved Research Plan
What does ICH GCP (R3) say?

- **2.5 Compliance with Protocol**
  - 2.5.3 The investigator should document all protocol deviations. In addition to those identified by the investigator themselves, protocol deviations relevant to their trial participants and their conduct of the trial may be communicated to them by the sponsor … In either case, the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable …

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Deviations from the IRB-approved Research Plan
What does ICH GCP (R3) say?

- **3.9.3 Sponsor Oversight**
  - The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or wellbeing.

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Deviations from the IRB-approved Research Plan
What does FDA say?

- [A Protocol deviation is] "any change, divergence, or departure from the study design or procedures defined in the protocol."
- **Important Protocol deviations**: "A subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being."

FDA adopts this definition from ICH E3 (R1):
Structure and Content of Clinical Study Reports

FDA Draft Guidance, Dec 2024: Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices

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Deviations from IRB-approved Research Plan
What does BMC/BU Med Campus HRPP say?

- **Deviations** represent incidents, circumstances or processes that occur during the research that are not part of or are inconsistent with the approved IRB study plan, HRPP policies and procedures, or Federal regulations.
  - **Major deviation:** Deviations that *could* negatively affect
    1) subject safety/well-being; OR
    2) integrity of the data
    - Must be reported to the IRB asap and within 7 days of when the PI/study team becomes aware of the deviation (Ceded studies will follow IRB of record's policies for reporting)
    - Must assess whether a deviation can also be an Unanticipated Problem (UP)
  - **Minor deviation:** Deviations that are less impactful – less risk to subject safety or integrity of the data
    - Should be documented, compiled, reviewed and submitted to the IRB at the time of the progress report (as part of Continuing Review)

HRPP Policy 6.6.5.1
Classification of Deviations

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Are these scenarios deviations?

1. The site delegation log is missing a signature of one of the study staff members.

> **Not a deviation.** This comes from ICH GCP guidance, but typically signatures on the delegation log would not be described in the protocol or other elements of the research plan.
>
> The study team should be instructed to correct this omission.

2. There are several study team members on the site delegation log tasked with doing clinical procedures that require license (which they do not have); source records confirm they have been doing these procedures.

> **Deviation.** Information such as qualifications to do certain critical study procedures will typically be described in the protocol.
>
> The study team should document the deviation. This would be considered a "Major" deviation (or using FDA's terms "Important" deviation, as it has possibility to adversely impact participant safety/rights/welfare as well as the reliability of the study data.

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Protocol Adherence: Common Types of Deviations

- Enrollment of ineligible participants
- Recruitment and screening methods
- Consent forms
- Consent processes
- Insufficient documentation
- Study visit procedures and windows
- Who can carry out certain procedures
  - If specified in protocol, institutional policies, or other applicable requirements)
- Safety monitoring and reporting
- Data collection, storage, security

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You would like to enroll Spanish speakers but your study is approved to enroll English speakers only.

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To be eligible, hemoglobin must be >12.5% as determined by Eligibility labs. Due to an error in processing the eligibility hemoglobin result was not done. The patient had a clinic visit last week and that hemoglobin result is available. The enrollment visit is in 3 days. What should the study team do?

Your response is anonymous.

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Your safety monitoring plan calls for review of all Adverse Events (AEs) every three months by the independent safety monitor. Since there were only minor AEs so far the PI decided to hold off on the Safety monitor review for now.

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On a "self-audit" of your study records, your coordinator realizes that there is no documentation of pregnancy testing results. She states that the pregnancy testing was done just not documented.

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Inclusion criterion: Subjects cannot be immunocompromised or have received immunosuppressive therapy w/in 30 days. A potential subject received an immunosuppressive drug infusion a week ago. The sponsor says this drug infusion will not increase risks to the subject. What should the team do to enroll this subject?

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The study is approved to enroll subjects 18 to 64. You want to include a potential subject who just turned 65.

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The reporting timeframe to the sponsor is reporting any SAE within 24 hours of being aware of the SAE. A subject called to report an SAE on Friday afternoon. The study doctor assessed the SAE on Friday night and it was reported to the sponsor on Saturday.

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You realize an outdated version of the consent form was used.

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Reasons why a protocol isn't followed

- Insufficient training
- Protocol is a static document while processes may evolve
- Insufficient assessment of competency of individuals in performing the delegated tasks
- Insufficient or inappropriate delegation of study tasks and procedures
- Insufficient PI oversight
- Complexity of protocol and/or certain procedures
- Elements of the protocol are unnecessarily rigid, making it difficult to comply
- Inexperienced PI and/or research staff
- Elements of the protocol that are not frequently done
- No written "work-flows" or internal processes developed by the research team to ensure THE THING is consistently done each time (regardless of individual doing it)

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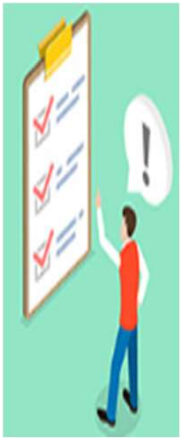
Managing Deviations



- Once identified, document and assess deviation(s)
- Deviations will need to be reported to the IRB, and as applicable Sponsor and FDA
- If "Minor" deviation, submit a list of all deviations to the IRB at the time of continuing review
  - Check Sponsor requirement for timeframe of minor deviation reporting
- If "Major" deviation:
  - Must assess as to whether it's an Unanticipated Problem (UP)
  - Submit to IRB within expedited timeframe (check IRB of record)
    - BUMC/BMC policy is submission of Reportable Events and New Information (RENI) within 7 calendar days
    - Within the RENI must develop Corrective and Preventive Action Plan (CAPA)
  - Check Sponsor timeframe for reporting of major deviations
  - If the PI is the Sponsor (holds IND/IDE) then must report to FDA

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Reporting Major Deviations (BUMC/BMC)

- **Reportable Events and New Information (RENI)**
  - Form in INSPIR which should include explanation of what happened & why
- **Corrective and Preventive Action Plan (CAPA)**
  - Describes how the deviation will be corrected now and prevented in the future
  - Use CAPA template (on IRB website)
  - Make sure your CAPA includes:
    - Best assessment of root cause(s)
    - Training of staff (including documentation of that training)
    - Evaluation to make sure your corrective/preventive actions actually did or will correct the problem (and documentation of that evaluation)
    - How will the PI ensure adequate oversight of study procedures

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Promoters of Protocol Adherence

- FDA: Thoughtful protocol design can help to minimize important protocol deviations.
- In considering your study design and writing a protocol, (or reviewing to accept taking part in a study), ensure it includes sufficient flexibility regarding conduct and procedures (such as eligibility criteria, visit windows, etc.)

"Clinical trials should be described in a clear, concise and operationally feasible protocol. The protocol should be designed in such a way as to minimize unnecessary complexity and to mitigate or eliminate important risks to the rights, safety, and well-being of trial participants and the reliability of data. Protocol development processes should incorporate input from relevant interested parties, where appropriate. Building adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, can reduce the number of deviations or in some instances the requirement for a protocol amendment. Such adaptability should not adversely affect participant safety or the scientific validity of the trial."

ICH E6 (R3) Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

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Promoters of Protocol Adherence

- All research team members: Read the protocol. Read it again. And again! In full.
- Operationalize the protocol
  - All study visits and interactions with participants
  - Who will do what activities? How will the activities be carried out?
  - What data will be collected at the interactions?
    - Create source data collection forms as necessary

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Promoters of Protocol Adherence

- Institute formal protocol and task-specific training for team members
  - Before starting the study
  - With each amendment
  - For complex and/or infrequent procedures, review the process periodically to ensure staff are ready
  - For managers: make sure staff assigned to do a task are fully trained, observed, and assessed for competency
- Schedule a formal protocol review X* times per year. Critically assess if study procedures (which can "evolve" over time) have changed

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Promoters of Protocol Adherence

- Make sure to document all protocol deviations;
  - Review deviations on-going for possible effects
  - For any that could affect quality or safety, make a plan to prevent recurrence

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Key Points to Remember…

"Adherence to protocols is first line of defense in protecting human subjects from harm."

(OIG Report on FDA Oversight of Clinical Investigators, 6/2000)

Know your protocol and follow it.

Protocol adherence is how we protect participants and ensure that the data we work so hard to generate are credible, reliable, and ultimately …. USABLE.

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