The Importance of Following the PROTOCOL in Clinical Trials
Upon completion of this presentation, participants will be able to:

- Describe the following terms: Protocol, Protocol Deviation, Protocol Violation, Form FDA-1572, Protocol Exception
- Understand the importance of following the clinical trial protocol to exact specifications
- Create a list of questions that should be answered by the sponsor or trial organizers prior to patient enrollment.
ICH Guidelines, E6: Good Clinical Practice

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

PROTOCOL: Definition

21 CFR Part 312.23
A protocol must contain:

• A statement of the objectives and purpose of the study.

• The criteria for patient inclusion / exclusion as well as an estimate of the number of patients to be studied.

• A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

• The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

• A description of the observations and measurements to be made to fulfill the objectives of the study.

• A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

21 CFR 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized to receive it.

Sec. 312.60 General responsibilities of investigators.

An investigator is responsible for the control of drugs under investigation.

Sec. 312.62 Investigator recordkeeping and record retention.

Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.

21 CFR 312.60: General responsibilities of investigators

• Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations;

• Protecting the rights, safety, and welfare of subjects under the investigator's care;

• Obtain the informed consent of each human subject to whom the drug is administered.

Signed Investigator Statement

Form FDA-1572

• Statement of the investigator
  – Submitted to FDA by the sponsor
  – Must be signed by the investigator
  – Contains the name and address of the IRB, all clinical labs and locations at which the study will be conducted
  – Lists subinvestigators who are under the supervision of the primary (principal) investigator

Signed Investigator Statement

“I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subject.”

## Statement of Investigator

*(Title 21, Code of Federal Regulations (CFR) Part 312)*

(See instructions on reverse side.)

### 1. Name and Address of Investigator

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### 2. Education, Training, and Experience that Qualify the Investigator as an Expert in the Clinical Investigation of the Drug for the Use Under Investigation. One of the following is attached.

- [ ] Curriculum Vitae
- [ ] Other Statement of Qualifications

### 3. Name and Address of Any Medical School, Hospital, or Other Research Facility Where the Clinical Investigation(s) Will Be Conducted.

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21 CFR 312.53 Selecting investigators and monitors

• Select only investigators qualified by training and experience as appropriate experts to investigate the drug.

• Ship investigational new drugs only to investigators participating in the investigation.

• Ensure the investigation is in accordance with the IND

Protocol DEVIATION: Definition

- Variation from processes or procedures defined in a protocol.
  - Does not preclude the overall evaluability of subject
  - Does not affect the safety of subject
Examples of a protocol deviation.

- Patient has lab values outside the range listed in the protocol for eligibility.
- Protocol says images must begin 15 +/- 5 minutes post injection but begins at 22 minutes.
Protocol DEVIATION

• The number of protocol deviations should be minimal
  – Where clinical or technical situation varies from the protocol due to circumstances beyond your control
  – Protocol deviations that involve safety measurements should be reported to the IRB

• Protocol deviations should **not** take place in situations where you simply want to do things differently
Protocol VIOLATION: Definition

• A significant departure from processes or procedure

• May affect the evaluability of the data
Protocol VIOLATION: Examples

• Some examples of Protocol Violation
  – Changing technical parameters of the acquisition
  – Enrolling an ineligible subject
  – Improper informed consent
Example 1

• You are supposed to inject 10 mCi per protocol, and due to the radiopharmacy processing you only have 7.5 mCi in the syringe. What do you do?
  – Depending upon the study, the sponsor may provide a protocol exception, or may instruct you to not use that dose because it is too low.
  – Do not simply inject just because the patient is on the table!
  – If the sponsor allows the exception, make sure you have the sponsor provide official documentation stating that it was ok to inject the lesser amount.
Avoiding Deviations & Violations

• If a technical “glitch” causes a protocol deviation that is out of your control, document the situation in writing (note to file): what happened, what you did, and why you did it. Always include your signature and the date.
Avoiding Deviations & Violations

• Provide education and written information to all imaging technologists that may be participating in the scanning of a research patient.
  – This will help reduce deviations and violations of the protocol.
  – Source documentation will be standardized
  – Sponsor’s expectations will be met
Avoiding Deviations & Violations

• Provide a copy of the protocol and technical manual to the technologists in addition to keeping a copy in the department.
  – Reinforce the importance of quality imaging data.
  – Worksheets and checklists are recommended
Avoiding Deviations & Violations

- There may be a long period of time between scanning study participants.

- Prepare prior to the participants arrival.
Avoiding Deviations & Violations

• If the study protocol is standard of care imaging:
  – It is still important to identify the patient as a study participant.
• If the study protocol is not standard of care imaging:
  – Review the protocol and the imaging manual.
  – Have all case report forms that need to be filled out at the time of the scan readily available.
  – Confirm the participants appointment and the time of the delivery of the radiopharmaceutical.
Protocol AMENDMENT: Definition

**ICH Guidelines, E6: Good Clinical Practice**

**Protocol Amendment:** A written description of a change(s) to, or formal clarification of a protocol.

21 CFR 312.30 Protocol Amendments

A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Examples of changes requiring an amendment under 21 CFR 312.30:

• Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

• Any significant change in the design of a protocol (such as the addition or dropping of a control group).

The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

Protocol AMENDMENT: Definition

• Amendments (and revised consent forms) must be approved by the IRB prior to implementation
  – Exception: administrative or clerical amendments can be submitted to the IRB as informational only
• Amendments are submitted to the FDA by the sponsor
• Amendments are submitted to the investigator in writing
Site Participation

• Prior to a site participating in a sponsored clinical trial, a general discussion should take place between the sponsor and the imaging personnel.

• The aim of this discussion is to assess whether the site is capable (i.e. equipment and/or personnel) of properly conducting the study procedures.
Site Participation

- This discussion (or questionnaire) may include information regarding:
  - Site information (address, email, fax, phone)
  - Site equipment (scanner, radiopharmacy, phantoms, collimators)
  - Investigator/personnel
  - Regulatory requirements (lab certifications, CVs and medical licenses)
  - Research experience (Phase 1, 2, 3)
  - HIPPA compliance
  - Medical records policies
Feasibility Examination

- Imaging personnel should carefully review the protocol for details on technical procedures.
- Does the protocol detail the:
  - Scanning parameters
  - Quality control procedures (e.g., calibration)
  - Imaging and radiopharmacy equipment required
  - Specimen handling required (e.g., blood samples)
  - Specialized equipment required (e.g. well counter, centrifuge)
Questions to consider:

• Does your site have the proper personnel and equipment to participate in the clinical trial?

• It is **not** enough to simply say “yes, we do PET/CT” in response to a question about whether you can do a sponsored clinical trial!
What questions do I ask?

• Do I have to qualify my PET or PET/CT scanner?
• Can my site receive or produce the radiopharmaceutical used in the study?
• How long will the scans and QC take?
• Is there any specialized equipment (such as a biohazard freezer, centrifuge, well counter) required for the study?
• Who is responsible for labwork, ECGs, urine collection, or other study parameters?
What questions do I ask?

• How will I be transferring the image data and when does it need to be transferred (i.e. sFTP and within what time period)?
• What imaging data needs to be submitted (e.g., raw data or reconstructions)?
• What are the file naming procedures (i.e. PET AC, PET NAC, CTAC, etc.)
• What are the dose ordering procedures?
• What forms do I use to record data?
Sponsor-Provided Materials

- Protocol
- Technical manual(s)
- Forms/worksheets for source documentation and image transfer

- The advantages of a technical manual are:
  - Protocol amendments not required for changes
  - Ease of distributing a specialized document
  - Can be modified based on site-specific needs
Implementing the Protocol

- Reviewing the sponsor’s imaging protocol and/or manual is important to determine whether the scanning protocol makes clinical sense.
- The imaging data should provide information to support or answer the primary goals or the imaging endpoints of the study.
- If the principle investigator (PI) is not in the imaging department, such as oncology, close communication between department staff is required.
Implementing the Protocol

• What do you do if you have not been given ample opportunity to perform a thorough review of the imaging, QC, or radiopharmacy procedures?
  – Contact the sponsor, CRO, or imaging core lab.
  – Document all communication.
    • Emails
    • Memos
    • Telephone conversation
  – Keep the study coordinator in the loop.
Implementing the Protocol

- In addition to reviewing the sponsor’s protocol and imaging manual, review any CRF’s and source document worksheets that you may be responsible for completing at the time of the scan.
- A CFR (Case Report Form) is a paper or electronic set of questions that is used to collect data in a clinical trial.
- A source document worksheet is a place where you record raw data.
Implementing the Protocol

- Data that you may be required to provide:
  - Date of scan
  - Dose assay time (pre and post injection)
  - Net administered activity
  - Time of injection
  - Scan start time, end time
If any imaging data is found to be missing or if the data is inaccurate or inconsistent with the imaging protocol, a query or data clarification form may be sent by the sponsor.

A query may or may not be a protocol deviation or a protocol violation.

A query is used to obtain missing information or to clarify a portion of the imaging data received.
Queries and Data Clarification

A query may be sent due to:

- Date of birth in the DICOM header does not match the CRF.
- Missing images or incomplete submission
- Time of scan does not match protocol requirements
- Data is not anonymized in all DICOM headers
It is industry standard and imperative to document all correspondence between the site and the sponsor.

It is also good to document all correspondence with the imaging core lab if one is used for the trial.

Documentation includes:
- Email
- Memo
- Phone conversation
- Note to file
Communication

• It is important to include the study coordinator in all correspondence with the sponsor.

• Ways to keep the coordinator “in the loop”:
  – Courtesy copy on all emails
  – Courtesy copy on paper correspondence
  – Notify the coordinator of telephone conversations with the sponsor and the results
  – Include the coordinator in all scheduled teleconferences and meetings with the sponsor
• Don’t underestimate the time it will take for a research protocol.
  – Schedule adequate time for any ancillary procedures that need to take place in the imaging room (vitals, ECG, blood draws, etc.)
  – Inform front desk personnel about any specimen handling questions (such as a patient dropping off urine samples, questionnaires, etc.)
Departmental staff may be required to alter standard department procedures to accommodate a research study.

Staff may include:
- Schedulers
- Transporters
- Nurses
- Administrative
- Radiation safety
• Design a procedure that will notify the nuclear medicine department when a trial participant is scheduled to have their scan.
  – This will give the technologists enough time to perform any mandatory QC prior to the scan.
  – The protocol may require the lab to perform a cross-calibration between the PET scanner and the well counter within a certain amount of days of the scan (blood sampling protocol).
The protocol is a specific document that describes the clinical trial in detail.

Protocol amendments must be submitted to the IRB before they are implemented.

The investigator is responsible for making sure all patients provide written informed consent.

The investigator is responsible for control of the investigational product.
Summary

- Imaging procedures may be included in the protocol or a technical manual.
- Avoid protocol deviations and violations.
- Don’t change any protocol parameters without permission from the sponsor or the sponsor’s representative.
- Document everything, and communicate to everyone.