RESEARCH 103
Session 4:

Protocol and Study Measures Training - The Importance of Accuracy and Consistency

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The Purpose of a Protocol

- Describes the objectives, design, methodology, statistical considerations and aspects related to the organization of a study
- Purpose:
  - Ensures safety of human research subjects
  - Standardization – the same data collected in the same way for all subjects. Especially important in multi-site trials or studies with multiple personnel
  - Scientific integrity
- Must be IRB approved prior to implementation

Regulations/Guidelines

- ICH GCP E6 (6)
- FDA Regulations - 21 CFR 312, 812
- NIH applicants can use a template with instructional and sample text:
  - Phase 2 or 3 clinical trials that require Investigational New Drug applications (IND) or Investigational Device Exemption (IDE) applications
  - Behavioral and social sciences research involving humans
  - https://grants.nih.gov/policy/clinical-trials/protocol-template.htm

Protocol Components

- General Information
- Background Information
- Trial Objectives and Purpose
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Statistics
- Direct Access to Source Data/Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy

ICH GCP E6 (6)

Do all studies require a written protocol?

- No treatments involved, no sponsor, no NIH funding (ex. Sample/data repositories, record review, survey studies, etc)
  - Do we need a protocol?
- Some IRBs do require a separate protocol and some may require only an application.
  - IRB application questions based on protocol components
  - Writing up a protocol beforehand will help you think through study design, feasibility, logistics, biases, etc
  - A written protocol can be distributed to all personnel to ensure consistency
- Data from these types of studies may lay groundwork for other NIH-funded studies or be apart of an FDA application later
- May not be super elaborate!

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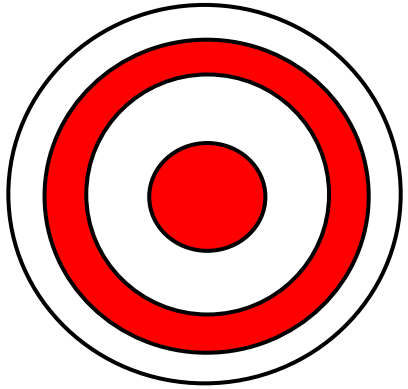
Feasibility

- Some things to consider:
  - How many staff members/investigators are needed?
  - Can all procedures be performed in one location?
  - Target patient population and enrollment number
  - Competing studies or too many studies being conducted simultaneously
  - Do you have access to all necessary equipment and resources?
  - Do you have adequate storage facilities for investigational product, supplies, and research records?
  - Length of a study

Feasibility

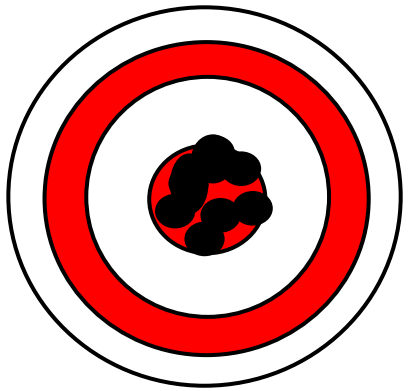
- Sponsored studies have site qualifications and initiation visits
  - Good time to discuss concerns about the protocol and/or feasibility issues
  - Investigators/sites may feel apprehensive about expressing concerns or declining a study
    - Will we be selected again if we decline this study?
    - Will expressing my concerns affect my relationship with the sponsor?

Difference between precision and accuracy



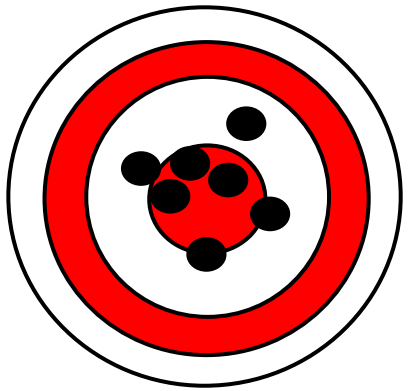
- Precision - measurement of the repeatability, or consistency, of a measurement.
- Accuracy - closeness of the measurements to a specific value
- Bullseye analogy:
  - Protocol is the bullseye

High Accuracy, High Precision



- Protocol followed for all subjects enrolled
- Same data points collected the same way for all subjects
- Does NOT mean that the outcomes and results will be as expected or favorable

High Accuracy, Low Precision

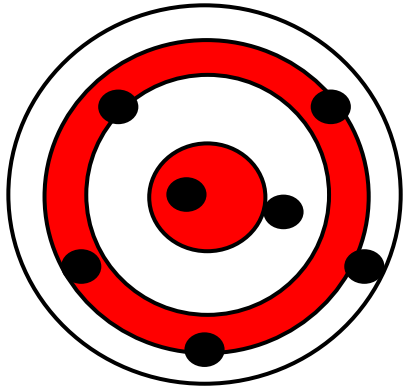


- Protocol followed for most subjects
- Maybe a few minor protocol deviations
- Expected part of the study due to unavoidable circumstances
- Data integrity maintained overall

Low Accuracy, High Precision

- Protocol is not followed, but consistent across subjects
- May be due to lack of understanding of the protocol, artifact of equipment
- Data integrity may or may not be compromised, depending on the nature of the deviations
  - Inclusion/exclusion criteria not met would be a major issue
  - Equipment errors may be major or minor

Low Accuracy, Low Precision



- Protocol is not followed, not consistent across subjects
- Could not make an inference from this data
- Major protocol deviations could potentially cause harm to the subjects

Protocol Deviations/Violations

- Protocol may outline how protocol deviations are going to be handled
- All deviations should be documented
- No universal definition for major vs minor. Usually determined by sponsor/IRB definitions.
  - Could it have caused harm to a subject?
  - Non-compliance of federal regulations?
  - Compromised data integrity?
  - Multiple minor deviations may culminate in a major violation if it compromises data integrity

Protocol Deviations/Violations

- May be immediately reportable to the sponsor and/or IRB depending on the nature of the violations and sponsor/IRB policies
  - May be reportable to FDA/OHRP
- Recurring protocol deviations
  - May require re-training of staff
  - Develop a corrective action plan
  - may mean that an amendment is needed

Protocol Amendments

- Amendment – a change to some aspect of the study
  - May be minor (e.g. administrative changes) or major (e.g. inclusion/exclusion criteria, extra visits, additional specimen collection etc)
- Must be IRB-approved prior to implementation
- If FDA-regulated product involved, also submit to FDA prior to implementation
- Amendments may change the risk/benefit ratio
  - May change approval categories under the federal regulations
  - May change IRB review status (expedited vs full board)
- Ensure all study staff and investigators are trained to new protocol to avoid protocol deviations!

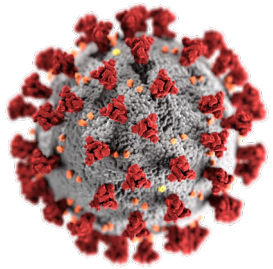
Amendments to the consent form

- Protocol changes may require changes to the consent form language which should also be IRB approved
- Should subjects be re-consented?
  - Sponsors/IRBs have policies about re-consenting
  - General rule of thumb: Could it change their willingness to participate?
    - Modified procedures, study design
    - Updates to safety information or confidentiality
  - What about people who have completed the study?
    - Should be notified of changes in safety profile or changes to the way their information/specimens are being stored or utilized
    - May be in the form of an addendum or letter

Changes to study operations

- Changes to site/institutional operations may not result in a change in study protocol, but may need to be IRB/sponsor approved if it changes the way you execute that protocol
  - Examples
    - Updates to site staff/investigators, updates to investigators status at a the institution
    - Updates to the delegation of authority log
    - Updates to financial disclosures
    - Changes to site location
    - Changes to storage/administration of investigational product
    - Alterations to the consent process

Changes to the clinical research landscape during COVID-19



- Sponsors and institutions were faced with tough decisions
- FDA Guidance document

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency
- Overall message: there is no universal answer for every study, every institution, and every patient.
- Revise study protocols and institutional policies as necessary to:
  - Protect patients
  - Maintain data integrity
  - Minimize protocol violations

Enrollment

- Do we continue to enroll, and if so, which ones?

Decision	Pros and Cons
Institutional suspension of all studies	• Pro: Allowed for focus on COVID • Con: Patients had less treatment options
Institutional suspension of “non-essential” studies	• Pro: Some drug/device studies could still enroll • Con: non-COVID PI-initiated studies suffered
Sponsor suspension of a study at all sites	• Pro: keeps all sites on the same level • Con: Sites may not find it fair, cost of maintaining study with no enrollments, extends length of study

Enrollment

- Some sites chose not to limit enrollment, but still saw reductions in study participation
  - Reductions in patients going to the doctor or seeking treatment
  - Restrictions on which procedures could be conducted and patients coming in for routine visits
- Studies that were close to enrollment goal before COVID closed enrollment early if statistical analyses could be made with current subjects.

Obtaining Consent

- Major challenge: staff not allowed on site or not allowed into restricted areas such as patient hospital rooms
  - e-consent
  - Telephone consent or use of a video conference call
- Sponsors/IRBs have specific policies about how this should be executed
- Federal regulations still apply!
- May require 21 CFR part 11-compliant systems

Treatments/Interventions

- Do we continue treatment, and if so, which ones?
- Do we change administration or study operations?
- Many patients did not feel comfortable going to clinic/hospital
- Discontinue treatment/intervention:
  - Is it safe? Follow-up safety visits likely needed
  - Can they get this treatment/intervention outside of the study?
- Continue treatment/intervention:
  - How do they receive the product?
    - Logistics: On site vs delivery to home or other location
    - With delivery, other things to consider like who's there to receive it, compliance, destruction, etc.

Treatments/Interventions

- Treatments/interventions that require on-site administration (e.g. infusions or non-portable devices)
  - Collaborating with another site who don't have as many restrictions may be an option
- Any change to the administration/utilization of these treatments would require a protocol amendment and IRB/sponsor approval

Study Visits

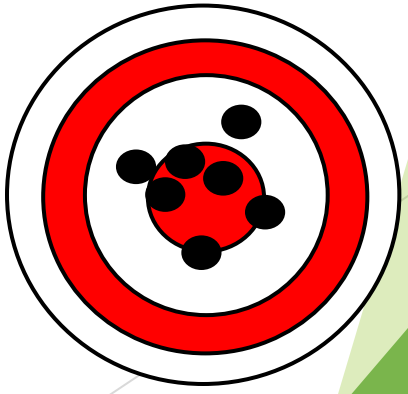
- Aside from receiving treatment, what about follow-up visits and other study procedures?
  - Most advised to conduct telehealth/telephone visits whenever possible
  - Labs, diagnostics, physical/neurological exams, other measurements more challenging
  - Collaborations with centers with less restrictions may be an option
- Would require Amendment/IRB approval

Monitoring

- Most institutions did not allow outside visitors
- Many sponsors suspended travel
- Remote monitoring challenges:
  - Limited/no access to medical records and study records
  - Staff not available or working from home
- Monitoring visits postponed or done out of window
  - Risk-based monitoring
- IT departments changed policies as time went on

Data and Documentation

- Expecting more protocol violations during this time
- Expecting more variability in data
- Any missed visits or incomplete data due to the pandemic should be documented in the research records.
- Changing methods or when amendments implemented should also be well documented
- May need to revise statistical plan or data analysis



Research Outlook – A new normal?

- A shift towards more and more electronic records and less paper
  - e-consent, e-regulatory, electronic systems
  - Becoming more secure
  - More systems offering part 11 compliant options
- Monitoring may be more of a hybrid of on site and remote
- Telephone/telehealth visits routinely part of protocols
- Protocols designed with more flexibility