Investigator Responsibilities

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NIH NATIONAL CANCER INSTITUTE

Essential PI Responsibilities…

- Responsible for the safe and ethical conduct of a clinical trial
- Evaluates the study proposal and decides on participation (for non-investigator initiated studies)
- Facilitates or verifies formal approvals according to regulatory requirements and ICH GCP
- Ensures that all site initiation activities are performed to start and conduct the study
- Participates in the selection of trial subjects according to the recruitment strategy

…Essential PI Responsibilities

- Performs or supervises the conduct of study-related procedures and monitors the safety of the trial subjects and investigational staff
- Collects accurate and verifiable data and other essential study documents
- Ensures compliance with regulatory requirements and ICH GCP, the protocol and the handling of the investigational product(s)
- Communicates with subjects, IRB, and sponsor staff
- Ensures adequate close-out of the study

Laws, Regulations and Guidances

- Laws
  - Legislative Branch (Congress)
  - Published in the United States Code (USC)
- Regulations
  - Executive Branch (Departments & Agencies)
  - Code of Federal Regulations (CFR)

BINDING

- Guidances
  - Agencies

Not Binding

Selected Regulations

- Title 45 Part 46
  - HSP regulations for HHS funded research
  - Interpreted by Office for Human Research Protections (OHRP)
- Title 21: FDA regulations
  - Part 11: Electronic records and signature
  - Part 50: Protection of human subjects
  - Part 54: Financial disclosure by clinical investigators
  - Part 56: Institutional review boards
  - Part 312: Investigational New Drug application
  - Part 812: Investigational Device Exemption

Selected Guidance Documents

- OHRP: *Investigator Responsibility FAQs*
- FDA: *Protecting the Rights, Safety, and Welfare of Study Subjects (2009)*
- ICH Good Clinical Practice (GCP) Guidelines (2016)

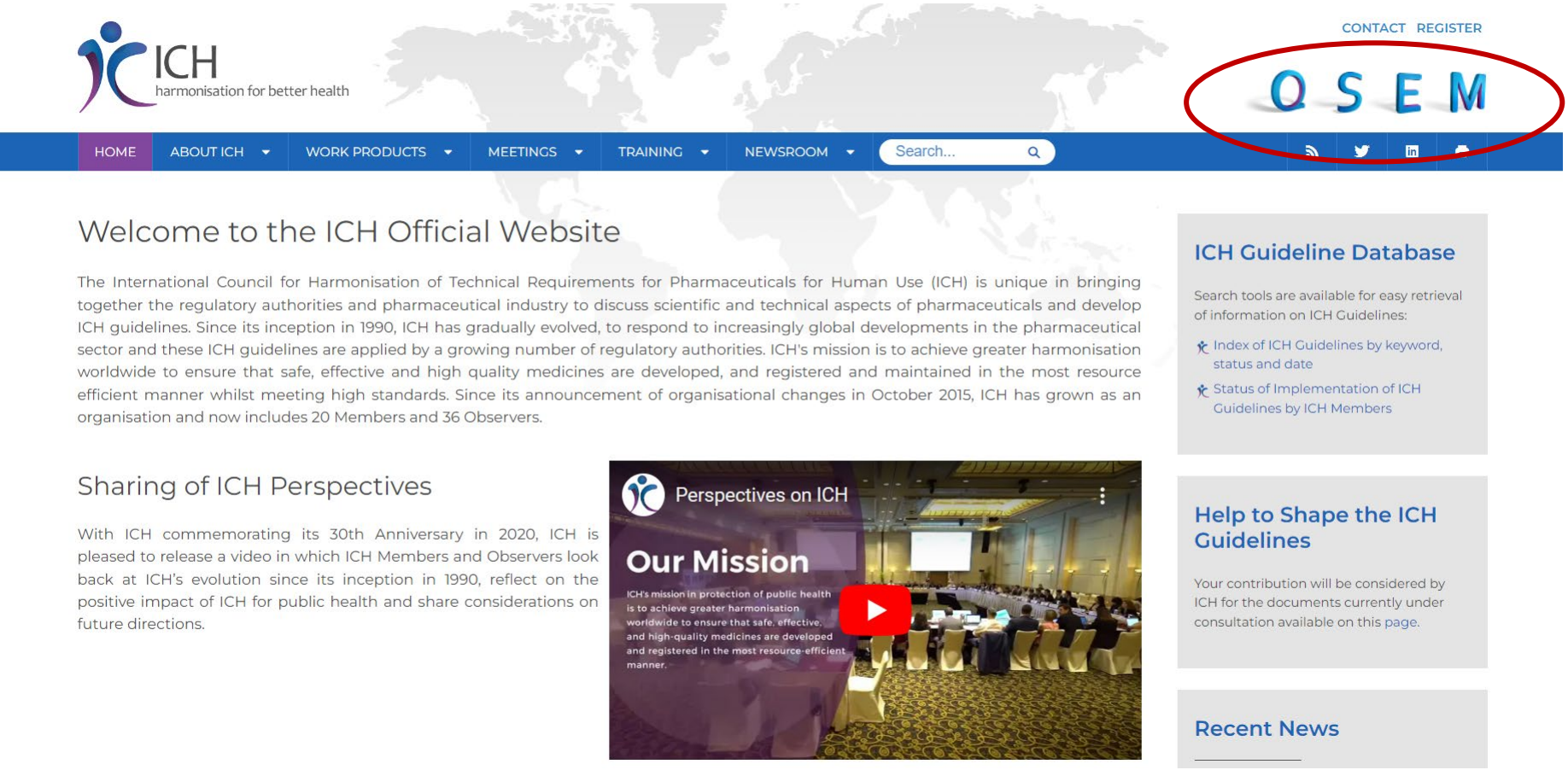
NIH Policies and Resources

- Policies:
  - Series 300
  - 500
  - 501
- *NIH Investigator Manual for Human Subjects Research*
- Presentation Archives
- NIH Investigator Seminar Series

International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- Drug regulatory authorities + representatives from pharmaceutical trade associations in Europe, Japan, U.S., Canada, and Switzerland
- Mission: to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.

ICH



https://www.ich.org/

ICH Standards

4 major categories of standards are:

- Quality guidelines
  - Chemical and pharmaceutical Quality Assurance
- Safety guidelines
  - in vitro and in vivo pre-clinical studies
- Efficacy guidelines
  - Clinical studies in human subject
  - E6: Good Clinical Practice (GCP) Guidelines
- Multidisciplinary guidelines
  - Cross-cutting topics that do not fit into one of the above categories

ICH GCP Guidelines E6(R2)

- International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Standards meant to ensure the rights and well-being of the patient are protected and quality data is provided
- 13 Basic Principles
- NIH protocols: Statement of Compliance
  - "The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) ….."

Sections of GCP Guidelines

- Glossary of terms
- Principles of ICH GCP
- Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
- **Investigator**
- Sponsor
- Clinical Trial Protocol and Protocol Amendment(s)
- Investigator's Brochure (IB)
- Essential Documents for the Conduct of a Clinical Trial
  - Site (AKA Regulatory Binder/File)
  - Sponsor

GCP and the Investigator

1. Investigator qualifications & agreements
2. **Adequate resources**
3. Medical care of trial subjects
4. Communication with the IRB
5. **Compliance with protocol**
6. **Investigational product**
7. Randomization procedures and unblinding
8. Informed consent
9. **Record and reports**
10. Progress Reports
11. Safety reporting
12. Premature termination or suspension of trial
13. Final report by Investigator

ICH GCP: Adequate Resources…

- Demonstrate adequate potential for recruitment
- Have sufficient time to properly conduct and complete the trial
- Have adequate staff and facilities to conduct the trial
- Ensure training for all persons assisting with the trial have adequate information about the protocol, investigational product and their trial-related duties and functions

…ICH GCP: Adequate Resources

- Ensure staff are qualified to perform those trial-related duties
- Supervise any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site

Recruitment and the Protocol

- Describe the various ways potential subjects will be recruited including any advertising
- Describe how potential participants will be identified and approached (where/when/how potential subjects will be recruited)
  - Specify which activities will be conducted to determine preliminary eligibility for the study including which activities will be performed **prior to the subject signing the research consent and after the consent is signed**.

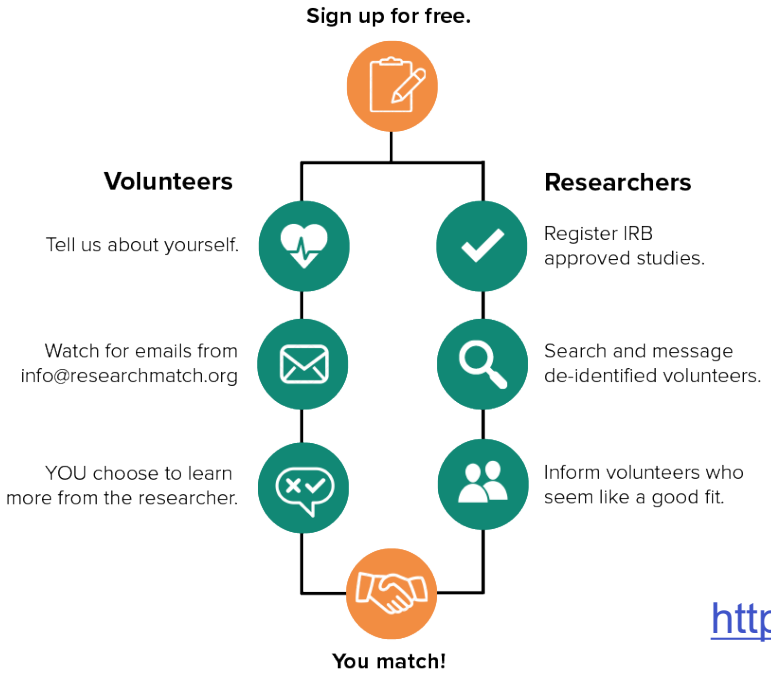
Patient Recruitment Services

http://intranet.cc.nih.gov/recruit/index.html

ResearchMatch

- Nonprofit program funded by the NIH
- Helps to connect people interested in research studies with researchers from top medical centers across the U.S.

volunteers	researchers	studies	institutions	publications
147,128	13,407	1,306	219	631



https://www.researchmatch.org/

Feasibility

- Definitions:
  - Capable of being done or carried out *Merriam-Webster*
  - Possibility that can be made, done, or achieved, or is reasonable *Cambridge Dictionary*
- Feasible comes from *faire*, the French verb meaning “to do”
- Do: to bring to pass or carry out, perform, execute, bring about *Merriam-Webster*
- Ultimately every study is “feasible” given enough time, money and resources but is every study “doable”?

Feasibility Assessment

- Conducted to measure the research site's potential for successfully conducting a study
- Includes an evaluation to conduct the study safely, ensure data integrity, stay within the budget and meet any predetermined timelines
- Includes assessing:
  - Study population
  - Protocol and procedures
  - Staff/staffing
  - Space
  - Budget
  - Data management
  - Monitoring

Interdisciplinary Collaboration

- Does the protocol require procedures that impact other disciplines (e.g., PT, respiratory, etc.)?
- Does the participant require support from other disciplines (e.g., social work, etc.)?
- How are research labs handled?

Delegation & Supervision

- Individuals who are delegated tasks:
  - Are qualified/licensed to perform the tasks
    - Credentialed per CC
  - Receive adequate training on how to conduct the delegated tasks
  - Understand the study
- Supervision by PI
  - Documentation that PI is involved in the ongoing conduct of the study
  - Documentation of PI supervision or oversight individual not in PI's employ

Protocol Training

- Initial
- Modification to protocol and/or consent
- What is your/your team process?
- How is training documented?

Delegation of Tasks Log

- Log that allows PI to note delegation of research related tasks
- PI Tasks delegated based on:
  - Training
  - Licensure
- Completed prior to the initiation of any study-related tasks and procedures
- Updated as staff leave or are added
- Separate log for each study
- Include who will be able to cover for PI

Example Delegation Log

Site Delegation of Tasks Log / Signature Log

Site: _____ **Protocol Number** _____ **Study Title:** _____

The purpose of this form is to serve as the 'Site Signature Log' and assure that the individuals performing study related tasks/procedures are appropriately trained and authorized by the Principal Investigator to perform the task/procedure. The PI will sign and date the log after discussing with the individual the tasks he/she is being delegated. Once the individual no longer has delegated responsibilities, the PI will enter the end date and initial and date the entry. This form should be completed prior to the initiation of any study-related tasks/procedures. *The original form should be maintained at the site in the study regulatory/study binder. This form should be updated during the course of the study as needed.* **Study Roles include: Principal Investigator, Research Nurse, Associate Investigator, Data Manager, Nurse Practitioner, Regulatory Specialist**

	Assume PI responsibilities when PI is unavailable	Obtain informed consent	Eligibility assessment	Perform history, physical exam	Review of labs	Prescribe study agent	IND drug accountability (investigational pharmacy rep)	Oral Drug Accountability (patient returns)	AE Assessment (severity /relationship to research)	Expedited Event Reporting	Protocol Specimen Shipping	Case Report Form (CRF) completion	Data/CRF QA	Regulatory Document /Binder Maintenance	**Other** (please specify):	**Other** (please specify):	
Name:	The PI is responsible for the study design and conduct including all delegated tasks.																Dates of Responsibilities Format: mm/dd/yy
Study Role: Principal Investigator	Signature:						Initials:		Date (mm/dd/yy):			PI Signature: N/A				Date (mm/dd/yy): N/A	Start: / End: / PI Initials/ Date at End
Name:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Dates of Responsibilities Format: mm/dd/yy
Study Role:	Signature:						Initials:		Date (mm/dd/yy):			PI Signature:				Date (mm/dd/yy):	Start: / End: / PI Initials/ Date at End

Note: When there is a change in PI, a new log is needed.

FDA Warning Letter

You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]

> *"For [ ] protocol, you delegated the performance of protocol-specified clinical evaluations (e.g., physical examinations, and evaluation of signs and symptoms relating to a DVT or pulmonary embolism) to [ ] According to the Site Personnel Delegation Log, [ ] was assigned a role of data entry for CRFs. During the inspection, Mr.[ ] indicated that he was not trained or qualified to perform physical examinations, and other required assessments. For example…..*

ICH GCP: Compliance with Protocol

- Conduct the trial in compliance with the protocol
- Implement NO deviation from or changes to the protocol without agreement by the sponsor and prior IRB approval of an amendment
  - Exceptions:
    - When necessary to eliminate an **immediate** hazard to subjects
    - When the change is only logistical or administrative aspect (e.g., change in monitor, change of telephone number)
- Document and explain any deviation from the approved protocol
- May implement a deviation to eliminate immediate hazard to subjects without prior IRB approval but ASAP, the implemented deviation and reason for change should be submitted to the IRB and sponsor, if required.

FDA Perspective

- Failure to comply with the protocol may be considered a failure to protect the rights, safety, and welfare of subjects
- Non-compliance exposes subjects to unreasonable risk
- Includes:
  - Failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the test article poses unreasonable risks
    - Example: subject with decreased renal function and a trial in which decreased function is exclusionary because the drug may be nephrotoxic

Sponsors Eligibility Waiver

- Sponsor may grant an eligibility waiver (e.g., eligibility, dose change) if safe
- Contact medical monitor or CRA
- Should receive something in writing or a waiver number
- Receive IRB approval
- Considerations:
  - Will "ineligible" subject's data be used?
  - Will this skew the results?
  - What can the impact of this be for multi-site studies?

Wavier Denied – How to Access

- Expanded access IND may be possible
  - AKA: compassionate use
  - Requirements are stringent
- Applies to:
  - Individuals with serious or immediate life-threatening diseases/conditions who have no satisfactory alternatives
  - Approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS)
- IRB approval needed

Definitions

- Immediately life-threatening
  - Stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment
- Serious disease or condition
  - Disease or condition associated with morbidity that has substantial impact on day-to-day functioning

FDA Warning Letters...

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]

You failed to conduct the studies or ensure they were conducted according to the relevant, current protocols [21 CFR 312.60].

…FDA Warning Letters

"You failed to ensure that subjects met all protocol required eligibility requirements prior to enrolling the subjects into the study, and further failed to complete all protocol required screening and baseline procedures prior to randomization of subjects. Specifically, we note that 9 of 16 subjects enrolled at your site were ineligible and did not receive exemptions from the sponsor prior to enrollment …"

"The protocol required that subjects have baseline physical examinations performed. We note that subjects 001,095 and 129 did not have complete physical examinations performed as a part of their baseline evaluation."

"For the [ ] protocol, the required 13 day follow up visit for subject 7010 was not done due to reported scheduling conflicts; however, there is no documentation as to why an alternate date was not scheduled. The protocol required that on day 13, a physical examination with assessment of vital signs be performed, and blood samples be drawn for hematology and clinical chemistry."

ICH GCP: Investigational Product…

- Accountable for investigational product at the site
  - May be assigned to pharmacist
- Maintain records related to product:
  - Delivery to the trial site, inventory at the site and use by each subject
  - Subjects provided doses specified by the protocol and reconcile products received from sponsor
- Ensure that investigational product is stored as specified by sponsor or regulatory authority

…ICH GCP: Investigational Product

- Ensure that the investigational product is used only in accordance with the protocol
- Explain correct use of the investigational product to each subject and check, at intervals appropriate for the trial, that each subject is following the instructions properly

Investigational Drug Management and Research Section

- Provide research-related support including:
  - registration and control of all investigational drugs used for patients
  - aiding investigators in designing blinded studies
  - providing information on investigational drugs undergoing study at the NIH
- Investigational drugs must be registered with PDS before they are administered to Clinical Center patients
- Develop order sets in CRIS

Investigational Drug Control Unit

- Coordinates pharmacy activities for the entire cycle of studies from setting up to closure including:
  - Managing the investigational products for NIH intramural clinical trials
  - Facilitating investigational drug supply and inventory management
  - Assisting the PI and/or the NIH sponsor in developing protocol
  - Developing and updating preparation and dispensation procedures in accordance with the IRB approved protocols
  - Accommodating monitor and auditor visits
- IDCU policies

ICH GCP E6: Records and Reports…

- Maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects
- Ensure accuracy, completeness, legibility and timeliness of data to sponsor in CRF (data management)
- Maintain trial related documents

…ICH GCP E6: Records and Reports

- Ensure all financial agreements are in place prior to subject enrollment
- Provide access to records by monitor, regulatory agency or auditors

PI Responsibilities…

- Ensure research team members handling data are appropriately trained on data management and use of the protocol database
- Ensure that all source data is documented in the Medical Record/Research Chart with accuracy, completeness, and consistency
- Ensure the overall quality of the research data is verifiable and acceptable for sponsor submissions, publications, etc.
  - Ensure accuracy, completeness, legibility and timelines of the data
  - Review of data entered into database

…PI Responsibilities

- Review data discrepancy/clarification resolutions for accuracy, consistency and timely response
- Review audit/monitoring reports and responses
- Data analysis
- Reporting results to clincialtrials.gov

Additional Responsibilities

- Coverage
- Referring provider communication
- Routine/weekly meetings
  - Minutes
  - Attendees
  - Topics
    - General protocol information
    - Subjects on study
    - Subjects being screened
    - Adverse events and other reportable events

Adverse Event (AE) Assessment

- Done by the investigator with input from the research team
- Determine
  - Event term
  - Severity of event
  - Seriousness of event
  - Attribution of the event

Determining Attribution…

- What is already known about:
  - Drug or classification of the drug
  - Therapy or intervention
  - Expectedness
- Is there a temporal relationship of the AE to the study intervention?
- Does the AE improve or disappear when the intervention is discontinued?
- If re-challenged with the intervention, does the AE reappear?
  - At the same severity?
  - At the same time point?

… Determining Attribution

- Is the AE a result of existing disease signs and symptoms?
- Is the AE a result of existing baseline signs and symptoms?
- Is the AE a result of an underlying concurrent medical condition(s)?
- Is the AE a result of an underlying concurrent medication(s)?

Attributions: Approach 1

When having two options, the choices are typically:

- Related: reasonable causal relationship between the AE and _____
- Not related: no reasonable causal relationship between the AE and _____

Attributions: Approach 2

When having five options, the choices are:

- Definite—*clearly* related to _____
- Probable—*likely* related to _____
- Possible—*may* be related to _____
- Unlikely—*doubtfully* related to _____
- Unrelated—*clearly* not related to _____

Fill in the Blank for Approach 1 & 2

- Trick is filling in the “blank”
- IRB is looking for relatedness to the research
- Sponsor is looking for relatedness to the product
- Teasing out the attribution will assist in assessing the need to report the AE to regulatory groups

Association of Clinical Research Professionals (ACRP)

- International association
- Established in 1976
- Target clinical research professionals in industry and in hospital, academic medical centers and physician office settings
- Provide education and networking
- Certification for PI
  - Certified Principal Investigator (CPI®)

CPI Content Outline

- Scientific Concepts and Research Design (17%)
- Ethical and Participant Safety Considerations (25%)
- Product Development and Regulation (10%)
- Clinical Trial Operations (GCPs) (15%)
- Study and Site Management (23%)
- Data Management and Informatics (10%)
- PI Handbook
  - https://www.acrpnet.org/download/pi-certification-handbook/

QUESTIONS

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www.cancer.gov/espanol