Introduction to Clinical Research **Boot Camp 2021**

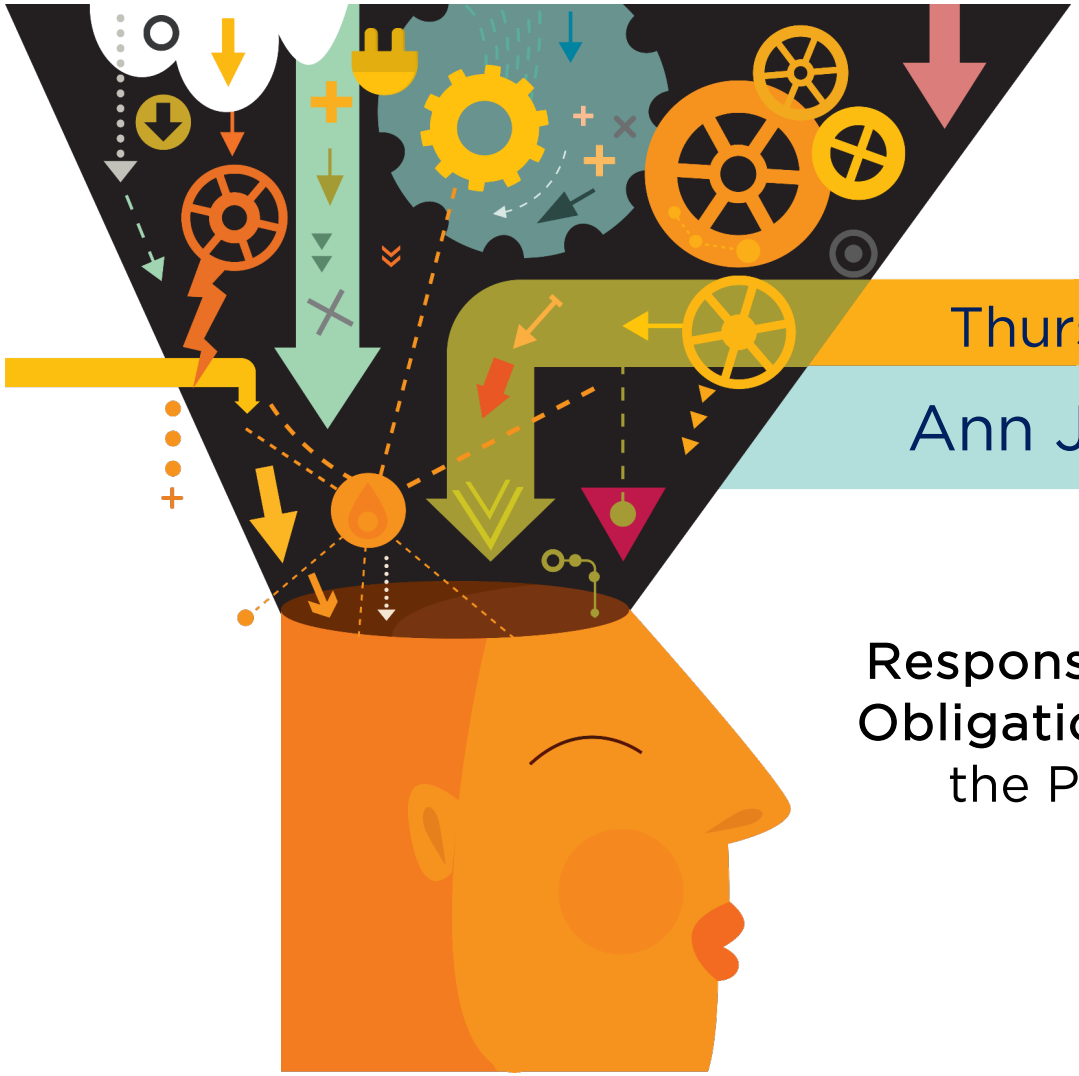
Investigators

July 26-30

12:00-1:00pm PDT

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.



Thursday, July 29, 2021

Ann J. Melvin MD, MPH

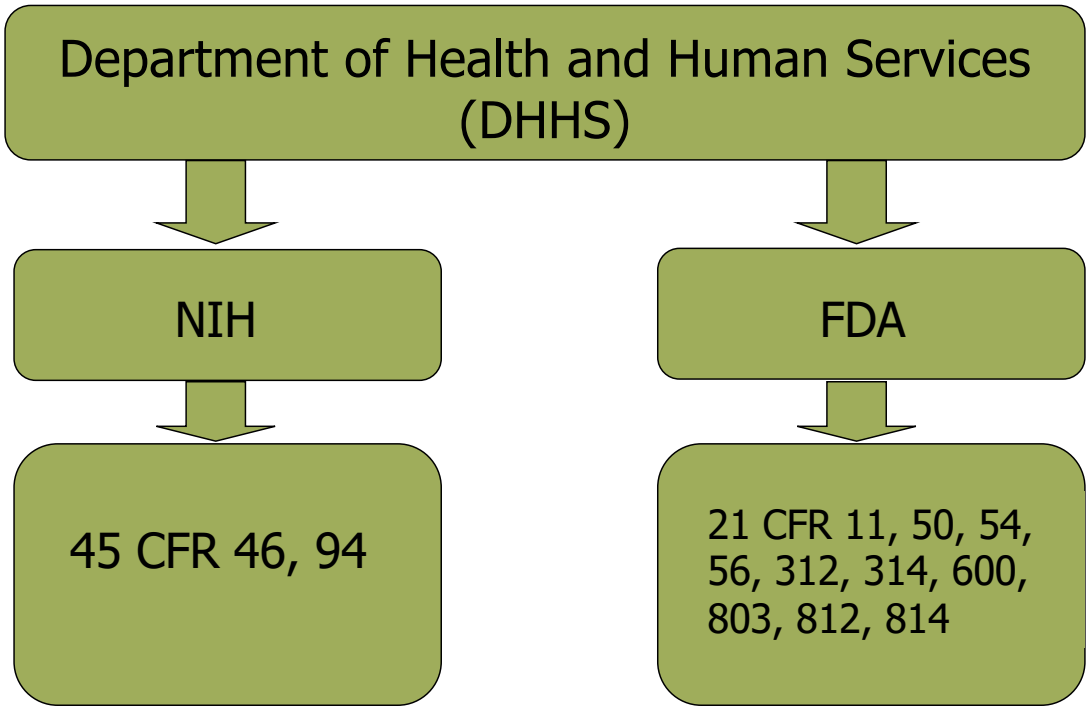
Responsibilities and Oversight Obligations: The Critical Role of the Principal Investigator

Learning Objectives

By the end of this session, you will be able to:

- Discuss the level of responsibility of the principal investigator to oversee clinical research projects
- Describe how to operationalize tools to meet the training and oversight needed for your study (checklists, logs, templates)
- Discuss best practices for accomplishing adequate supervision despite tight timelines, competing priorities, and limited resources.

Federal Regulation of Clinical Research



Investigator Responsibilities

- Conduct the study in accordance with the protocol, except when necessary to protect the safety, rights or welfare of subjects
- Personally conduct or supervise the investigation
- Inform subjects drugs are being used for investigational purposes and ensure informed consent and IRB requirements are met
- Report Adverse Events to the sponsor/IRB
- Read and understand the investigator's brochure

FDA Form 1572

Investigator Responsibilities

- Ensure that all associates, colleagues, and employees assisting in study conduct are informed about their obligations
- Maintain adequate and accurate records
- Obtain initial and continuing review and approval from the IRB. Promptly report to the IRB all changes in the research activity and all unanticipated problems and make no changes in the research without IRB approval
- Comply with all requirements regarding obligations of clinical investigators [21CFR 312]

FDA Form 1572

Lack of Adequate Trial Supervision Results in:

- Poor data
- Frustrated staff
- Study delays
- Risk to subjects
- Risk for audit by IRB/FDA/Sponsor

Case of the missing ECGs

- L.B. was the PI of a study for a new investigational agent. As the agent could cause prolonged QTc intervals, ECGs were required multiple times during the study.

- An FDA audit revealed that multiple ECGs were missing from several participants.

- FDA determination – the missing ECGs compromised subject safety.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm578987.htm

Case of the missing ECGs

- L.B. response:
  - ECG interpretation was delegated to a subinvestigator and only abnormal ECGs were brought to her attention.
  - ECGs were placed in a separate folder which she didn't review, so could have been misplaced or not done
  - When it was discovered that the ECGs had not been done, the subjects were pulled back to get an ECG and they were all unchanged from baseline

Case of the missing ECGs

- Was it acceptable for L.B. to delegate the reading of the ECGs to a subinvestigator?
- How could L.B. have been aware of the missing ECGs prior to the audit?
- How could L.B. have prevented this situation?

Case of questionable eligibility

- C.N. received a warning letter from the FDA after an inspection found multiple episodes of enrolling participants who did not meet eligibility criteria
  - Several patients did not meet requirements for statin dose at baseline
  - One participant was enrolled with a CK value that was out of range
  - Several patients were enrolled with out of range triglycerides.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm493102.htm

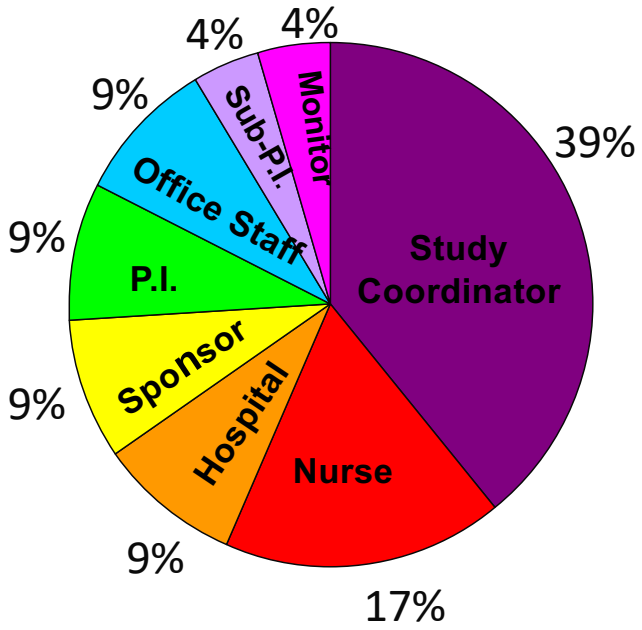
Case of questionable eligibility

- C.N. response:
  - None of the abnormal values were clinically relevant
  - The study coordinator received verbal approval from a study monitor to enroll the participants
- Do you think the FDA was satisfied with C.N.'s response?
- Can a study monitor OK enrollment criteria exceptions?
- How could C.N. have prevented this situation?

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm493102.htm

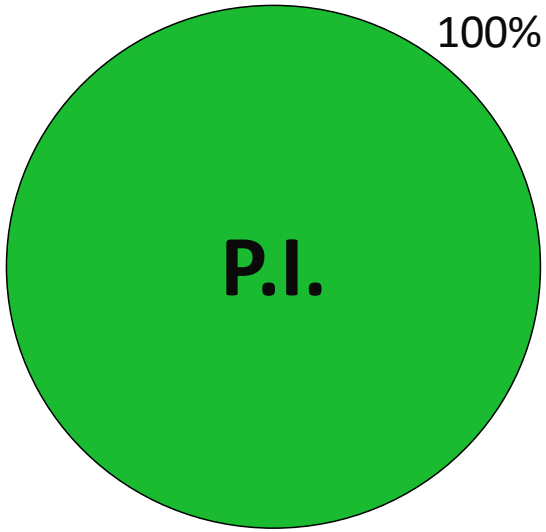
Blame for Poor Trial Conduct

Investigator's Report



n (parties blamed) = 23; n (cases) = 20

FDA/IRB/Institution Position



Woollen, S.W., CDER, FDA, 2000

So what does it mean to “personally conduct or supervise the investigation – I can’t do it all!”

How Can This Be Done?

- Appropriate delegation
- Adequate training
- Regular supervision

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What is Appropriate Delegation of Study-Related Tasks?

- The investigator should ensure that any individual to whom a task is delegated is:
  - qualified by education,
  - training
  - State licensure (where applicable), and
  - experience

  … to perform the delegated task.

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Are they qualified?

- Can a study coordinator process biologic samples?
- Is it acceptable for a study coordinator to grade abnormal lab values?
- Is it acceptable for a study coordinator to assign attribution to an adverse event?

How Can This Be Documented?

- Maintain a list of qualified persons to whom the study-specific task has been delegated
  - Describes the delegated tasks
  - Identifies the qualifying training
  - Identifies the dates of involvement in the study

Sample Study Specific Task Chart

Study task	Specific action	Responsible individual
Screen	Telephone screening of interested subjects	RC (name)
	Screening checklist	RC
Eligibility	Initial review w/ potential subject	RC
	Final eligibility assessment	PI
Consent	Obtain Informed Consent	PI/MD
Clinical Procedures	Blood draw	RN
	Interim History/Physical exam	PI/MD
Source Document	Source document for study data	RC & PI
	Data Entry	RC
	Review of source documents	RC
Toxicity Monitoring	Monitoring/review of AEs	PI

ITHS Research Resources

Signature List & Delegation of Responsibility Log

Principal Investigator:	
Study Title:	

Note: *Update this log in a timely manner as new personnel are added and/or study roles change.*

#	Staff Member Name	Staff Member Title ("co-investigator," "research coordinator," "data manager," etc.)	Staff Member Signature	Initials	Delegated Study Tasks (See key below)	Start Date	End Date
1							
2							
3							
4							
5							
6							
7							
8							
9							
	PI Signature:						

Delegated Study Task Key - Add or delete tasks as necessary to fit your study

1. Obtain consent	5. Dispense study drug/device	9. Submit and maintain IRB docs	13. Randomization	17. Staff education
2. Obtain medical history	6. Complete CRFs	10. Data monitoring	14. Blood draw	18. Data analysis
3. Perform physical exam	7. Handle CRF queries	11. Safety monitoring	15. Blood storage	19. Other
4. Assess eligibility criteria	8. Maintain regulatory docs	12. Advertising	16. Questionnaires	20. Other

What is Adequate Training?

- Have a general familiarity with the study and the protocol

- Have a specific understanding of the details of the protocol and the investigational product (if applicable), relevant to the tasks they will be performing

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What is Adequate Training?

- Know the regulatory requirements and standards for the conduct of clinical trials

- Are competent to perform the tasks that they are delegated

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Examples of Required/Recommended Training

- Human subjects protection training
- Good Clinical Practice training
- Protocol-specific training

If Someone Else Wrote the Protocol

- Read the Protocol
- Make sure everyone on the research team reads the protocol

Sample Training Documentation Chart

Study personnel	Specific study tasks performed	Type of training/ certification	Date of training
Research Coordinator (name)	Subject screening Maintenance of source documentation	HSP GCP Protocol specific training by PI	4/12/2016 7/5/2017 2/12/2018
Research nurse (name)	Study drug infusion	HSP GCP RN license Protocol specific training by PI	11/2/2017 3/7/2016 1998 2/12/2018

Making it clear

- Put their specific responsibilities on paper and give it to them.
- Review responsibilities and adherence at set intervals.
- When someone leaves make sure all new credentialing is done and Delegation of Duties log is updated

Tools and Templates

- Standard Operating Procedures
- Study Start-up Checklist
- Study Implementation Checklist
- Study Team Meeting Minutes
- Adverse Event Log
- Protocol Deviation Logs

ITHS Forms - https://www.iths.org/investigators/forms-templates/study-document-templates/

What is Adequate Supervision?

Set Aside The Necessary Time

- PI should have sufficient time to conduct and supervise the trial
  - Level of supervision should be appropriate to the staff, nature of trial and subject population
  - Don't take on more trials than you have time to supervise

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Conduct Regular Meetings With Staff

- Review basic science and clinical issues
- Review trial progress
- Update staff on any changes to the protocol or other procedures
- Review adverse events
- Review deviations/violations
- Keep minutes

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Pay Attention to Your Planned Informed Consent Process

- Review recruitment and approach procedures
- Assure that anyone who obtains consent* thoroughly understands the protocol
- Use of consent tools to document process

*consent can only be obtained by personnel with the training necessary to adequately explain procedures, risks, benefits, etc.

Study number _____ Version number _____ IRB date stamp _____

Date consent was signed _____ Time _____

_____1. Information about the study, including all available options, was provided in a language that the subject can understand.

_____2. The subject was given ample opportunity to consider all available options.

_____3. Questions were elicited and all answers given prior to signing consent.

_____4. The investigator or sub-investigator is comfortable that by providing adequate information to the subject there is no likelihood of coercion.

_____5. Verification of comprehension was done in one of the following ways (select at least one of the following):

____A) The subject asked relevant questions during the informed consent process.

____B) The clinician asked the subject specific questions about the study.

____C) The clinician asked the subject to repeat information discussed.

6. The following items were covered when discussing the informed consent for a study with the subject:

___a) The study involves research.

___b) Participation is voluntary

___c) Subjects can decide not to participate or withdraw at any time without penalty or loss of benefits.

___d) The purpose, duration of study, and issue of randomization/blinding

___e) The number of screening, pre-entry, entry and on-study visits.

___f) The length of follow up, what happens in case of early withdrawal, and the reasons for which a subject might be involuntarily discontinued from the study.

___g) Risks of study treatments and procedures, including psychosocial ones.

___h) Possible benefits, and if none, this should be stated.

___i) Reimbursement to subjects, if any.

___j) Costs to subject. What happens in case of research-related injury or side effects.

___k) What happens in case of pregnancy, if applicable.

___l) New findings will be communicated to them.

___m) Confidentiality of data.

___n) Phone numbers for questions at a later time, including research questions, questions related to subject's rights, and research-related injuries.

_____7. Copy of consent given to subject.

_____8. HIPAA consent signed, if required.

Comments:

Clinician signature _____ Date _____

What About Outside Parties?

- Who is considered responsible?

  Lab at local site

  Pharmacy at local site

  Central sponsor designated laboratory

  Staff not under PI's direct employment but working at local site – e.g nurse in the clinical research center

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What About Outside Parties?

- PI is considered responsible
  - Lab at local site or contracted by PI
  - Pharmacy at local site or contracted by PI
  - Staff not under PI's direct employment if working at local site
- Sponsor is considered responsible
  - Central laboratory retained by sponsor

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Protecting the Rights, Safety, and Welfare of Study Subjects

- During and following the trial, ensure adequate medical care is provided for any adverse events related to the trial.

- Clinical investigators should be available to subjects during the conduct of the trial at their site.

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Protecting the Rights, Safety, and Welfare of Study Subjects

- Failure to adhere to the protocol may be considered a failure to protect the rights, safety, and welfare of subjects.
  - Non-compliance with inclusion/exclusion criteria
  - Failure to perform safety assessments in a timely manner

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

Be Proactive

- Select qualified staff and ensure adequate training and supervision
- Write job aids, SOPs and check lists
- Walk through study visits – streamline/standardize activities as much as possible
- Have back-up plans –staff turnover-yikes!

Be Proactive

- Develop a QA plan
  - Real-time cleaning of data
  - Audit trails – should be clear what was changed, who changed it and why it was changed
- Pay attention to queries – do they indicate a system problem that should be addressed

Be Proactive - If You Are Writing the Protocol

- Make it simple, clear and easy to understand
- Write in reasonable flexibility
- Write a good safety and monitoring plan
- Determine which procedures can be done by non-physician staff
- Assure feasibility
  - Staff
  - Resources
  - Budget

Learning the hard way

- Personally review eligibility
- Review study conduct and data in real-time
- Understand the difference between research care and clinical care as it relates to the protocol
- Train, train, train
- Communication and team work

Setting up a mock study

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Impact of a Dietary Supplement on Muscle Function in the Elderly

- **Purpose:** To evaluate the safety, tolerability and efficacy of isoleupro in healthy older adults.

- **Background:** Decreased muscle strength with aging has been associated with increased risk for falls, pneumonia and a decreased quality of life. Isoleupro is a dietary supplement that has been shown to increase muscle mass in animal studies and is marketed to body builders. There have been rare reports of acute liver injury associated with the use of isoleupro, but it isn't clear if this is due to isoleupro or a contaminant, as isoleupro is frequently not the only ingredient in marketed products.

- **Primary objective:** To evaluate the 24 week safety and tolerability of isoleupro when given to healthy adults ages ≥ 70 – < 85 years of age.
- **Secondary objectives:** To evaluate the effect of 24 weeks of isoleupro on pulmonary function, 6- minute walk test and grip strength in healthy adults ages ≥ 70 – < 85 years of age.

- **Study population:** Adults from 70 years to less than 85 years of age without chronic cardiovascular, pulmonary, hepatic or renal disease.

- **Sample size:** 100 participants

Parameters	Screening	Baseline Visit 1[a]	Visit 2 (Day 14)	Visit 3 (Day 28)	Visit 4-7 (every 4 weeks)	Visit 8 (week 24)
Informed consent	X					
Pulmonary Function Tests	X			X		X
6 minute walk test	X			X		X
Inclusion and exclusion criteria	X					
Medical history	X					
Physical examination	X		X	X	X	X
Height and Weight	X			X		X
Laboratory – CBC, chemistry panel	X			X	X	X
Laboratory – serum biomarkers[b]		X		X		X
Laboratory – liver function tests	X	X		X	X	X
ECG	X			X		X
Vital Signs[c]	X	X	X	X	X	X
Study Product Dispensed		X	X	X	X	
Peak Flow Meter[d]	X	X		X		X
Grip strength		X		X		X
Review Exercise Diary		X	X	X	X	X
Quality of Life Questionnaires		X		X		X
Concomitant Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X

Learning Objectives

- Discuss the level of responsibility of the principal investigator to oversee clinical research projects
- Describe how to operationalize tools to meet the training and oversight needed for your study (checklists, logs, templates)
- Discuss best practices for accomplishing adequate supervision despite tight timelines, competing priorities, and limited resources.

Resources

- International Council on Harmonization (ICH) – 2018 Good Clinical Practice addendum:

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1

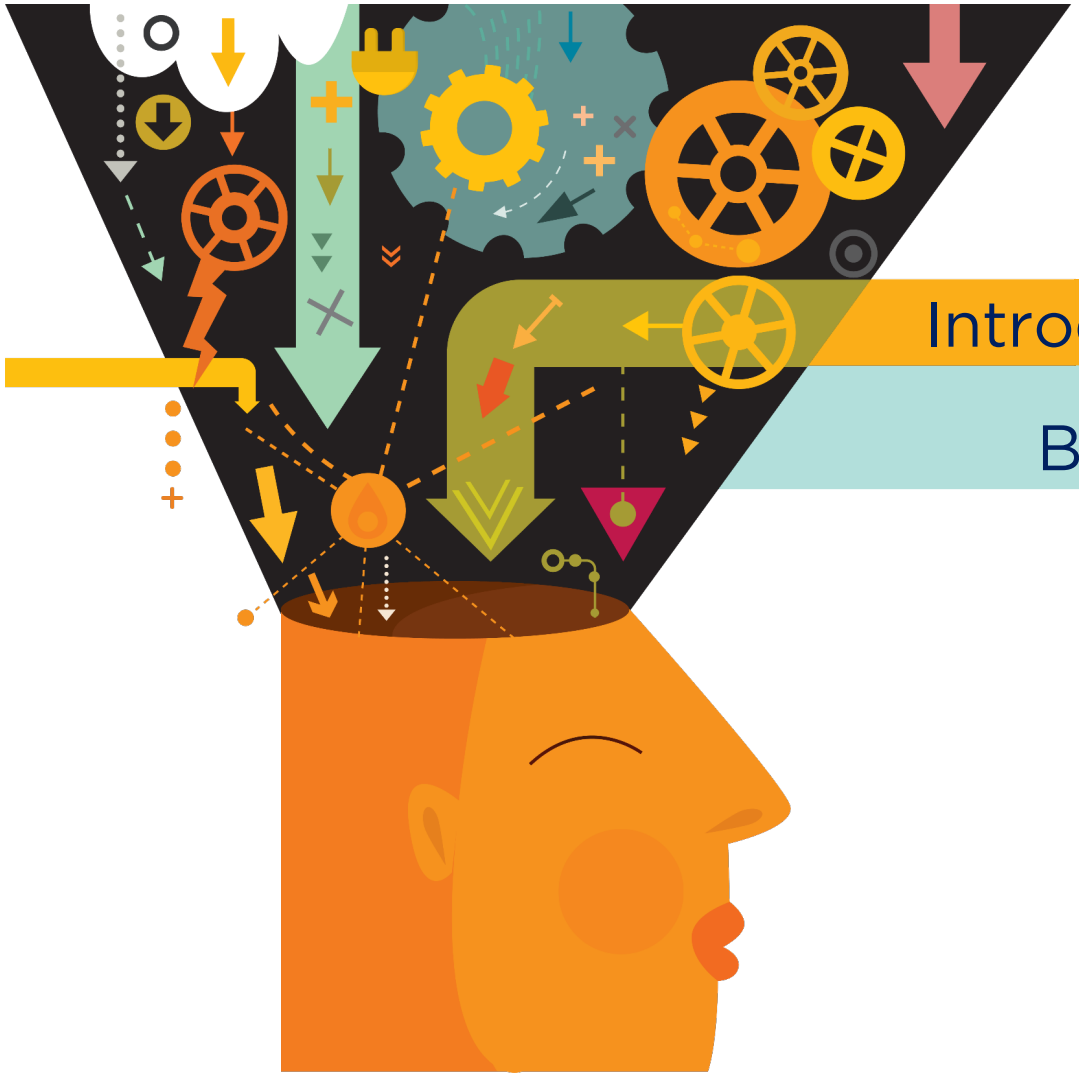
- FDA Guidance for Industry – Investigator responsibilities - protecting the rights, safety and welfare of study subjects:

  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Resources

- Institute for Translational Health Sciences (ITHS) www.iths.org
- Additional education http://www.iths.org/education
- ITHS clinical research handbook https://www.iths.org/investigators/handbook/
- Biomedical Sciences Toolkit – UW Healthlinks (search on "translational research toolkit") - UW login required http://healthlinks.washington.edu.offcampus.lib.washington.edu/
- PRIMER toolkit - http://researchtoolkit.org/
- Investigator Responsibilities – Regulation and Clinical Trials - https://www.fda.gov/files/science%20%26%20research/published/9-45---11-00-Investigator-Responsibilities---Regulation-and-Clinical-Trials.pdf

QUESTIONS?



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THANK YOU!