Research Professionals Network Workshop Series

Protocol Compliance

Michelle St. Paul, M.A.
Special Projects & IRB Manager
Framingham Heart Study
Boston University School of Medicine

Objectives

- Define protocol compliance;
- Review compliance standards;
- Discuss why protocol compliance is important;
- Discuss methods of demonstrating compliance; and
- Discuss when and why the protocol may be changed.

Defining the protocol and compliance

- A **research protocol** is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical **research** project.

So how do we define protocol compliance?

- Compliance is…adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

What standards must protocols adhere to?

- **Regulations and guidelines (e.g. OHRP, FDA**, HIPAA)
- Government sponsor (e.g. NIH Institute/center-specific policies)
- Industry sponsor policies
- Other Institution policies (e.g. when other institution is sponsor)
- State/local laws
- Institutional/departmental policies
  - **IRB policies (see BUMC/BMC HRPP Procedures & Policies)**
  - **IRB policies (see UVM RPO Procedures & Policies)**

- **ICH Good Clinical Practice (GCP)**

What are our standards?

Two groups maintain regulations guidance aka our standards for research protocols and their compliance.

OHRP
OFFICE FOR HUMAN RESEARCH PROTECTIONS

FDA U.S. FOOD & DRUG ADMINISTRATION

These regulations define:

- [human] subjects
- Interactions/interventions
- Sensitive information or materials

- AND provide standards for how all of the above must be treated, enacted, or protected

OHRP
OFFICE FOR HUMAN RESEARCH PROTECTIONS

FDA U.S. FOOD & DRUG ADMINISTRATION

Subjects

Human Subject (45 CFR 46.102 (e)(1)

- "… a living individual about whom an investigator conducting research obtains:
- **Information or biospecimens through intervention or interaction** with the individual and uses, studies, or analyzes those information or biospecimens;
- Or obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens."**

FDA Drug Study: Subject (IND regs)

–"…a human who participates in an investigation, either as a recipient of the investigational new drug or as a control." *21 CFR 312.3 (b)*

FDA Device Study: Subject (IDE regs)

–"…a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control." *21 CFR 812.3 (p)*

OHRP

OFFICE FOR HUMAN RESEARCH PROTECTIONS

- “[applies to]… all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research….”

- i.e. when the research is conducted or supported ($$) by the HHS you must adhere to these guidelines

- 45 CFR 46 - PROTECTION OF HUMAN SUBJECTS

HHS/OHRP 45 CFR 46

- Nuremberg Code, 1948
- Declaration of Helsinki, 1964 (WMA)
- Tuskegee Syphilis Study, 1932 –72
- Basic Regulations on Protection of Human Subjects, 1974 (DHEW)
- Belmont Report, 1979
- Protection of Human Subjects (Subpart A), 1981
- Common Rule, 1991
- New Final Rule, 2019

OHRP

OFFICE FOR HUMAN RESEARCH PROTECTIONS

- … all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research….

  aka

- when the research is conducted or support ($$) by the HHS

- 45 CFR 46 - PROTECTION OF HUMAN SUBJECTS

HHS.gov

U.S. Department of Health & Human Services

Office for Human Research Protections

About OHRP | Regulations, Policy, & Posting | Education & Outreach | Compliance & Reporting

News | Register IRBs & Obtain FWAs | SACHRP Committee | International

Office for Human Research Protections

The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP is part of the Office of the Assistant Secretary for Health in the Office of the Secretary of HHS.

OHRP provides clarification and guidance, develops educational programs and materials, maintains regulatory oversight, and provides advice on ethical and regulatory issues in biomedical and behavioral research. OHRP also supports the Secretary's Advisory Committee on Human Research Protections (SACHRP), which advises the HHS Secretary on issues related to protecting human subjects in research.

OHRP

Office for Human Research Protections

top

U.S. FOOD & DRUG ADMINISTRATION

- “[covers] …any experiment that involves a test article and one or more human subjects that… the results are intended to be submitted to FDA… as part of an application for a research or marketing permit…”

- i.e. when testing FDA regulated products (drug, device, or biologic) you must adhere to FDA guidelines

- 21 CFR 312, 812, 50, 54, 56 - Regulations: Good Clinical Practice and Clinical Trials

FDA (21 CFR 312, 812, *etc.*)

- Biologics Control Act, 1902
- Food and Drugs Act, 1906
- Federal Food, Drug and Cosmetic Act of 1938
- Kefauver-Harris Amendment of 1962
- Medical Device Amendment, 1976
- Protection of Human Subjects in Research, 1981
- ICH GCP 1996
- ICH GCP (R2) 2016

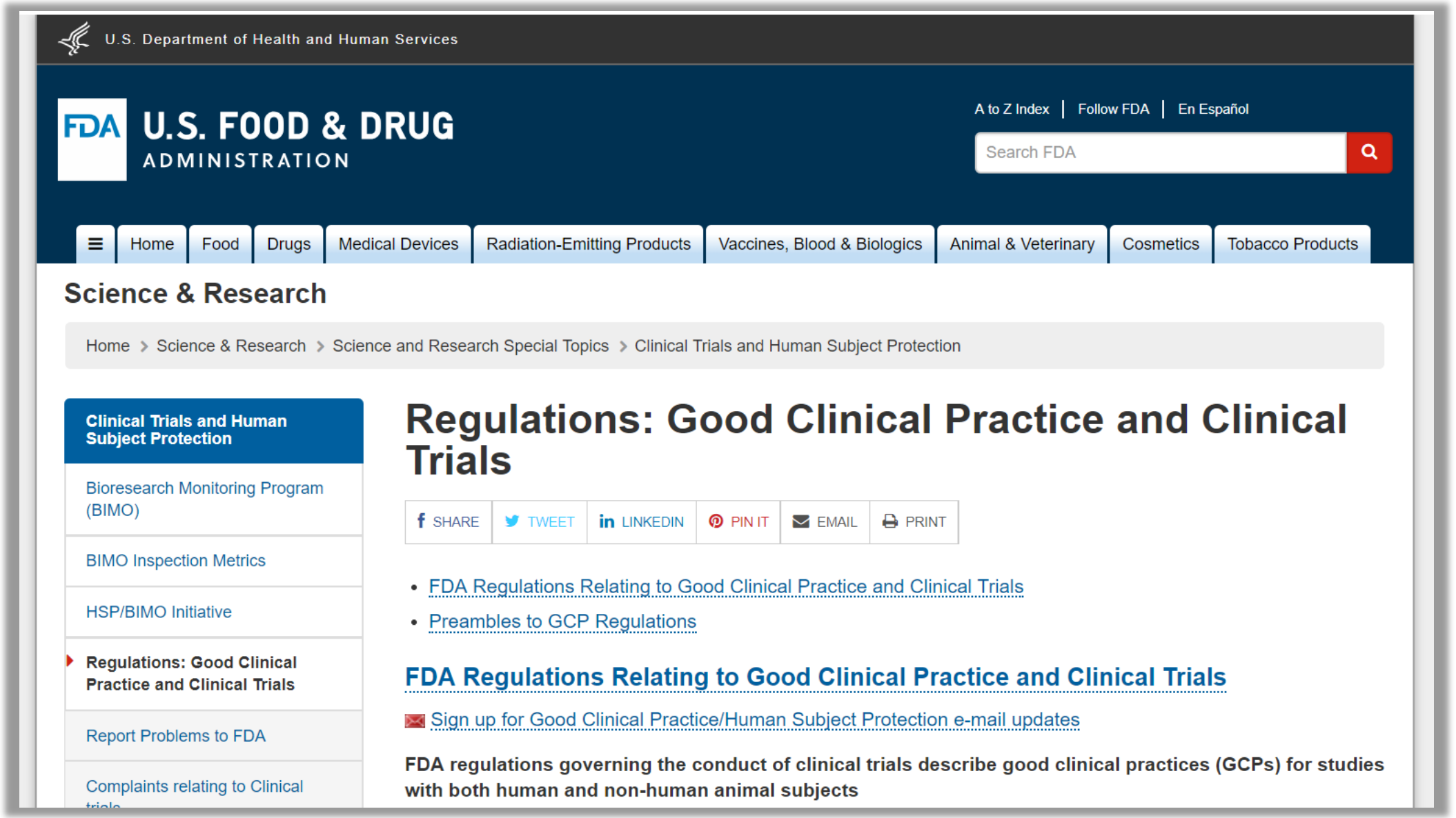
U.S. FOOD & DRUG ADMINISTRATION

- Clinical Investigation means any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act…or… the results are intended to be submitted to FDA… as part of an application for a research or marketing permit…"

  aka

- when testing FDA regulated products (drug, device, or biologic)

- 21 CFR 312, 812, 50, 54, 56 - Regulations: Good Clinical Practice and Clinical Trials


U.S. Department of Health and Human Services
FDA
U.S. FOOD & DRUG
ADMINISTRATION
A to Z Index | Follow FDA | En Español
Search FDA
Home
Food
Drugs
Medical Devices
Radiation-Emitting Products
Vaccines, Blood & Biologics
Animal & Veterinary
Cosmetics
Tobacco Products
Science & Research
Home > Science & Research > Science and Research Special Topics > Clinical Trials and Human Subject Protection
Clinical Trials and Human Subject Protection
Bioresearch Monitoring Program (BIMO)
BIMO Inspection Metrics
HSP/BIMO Initiative
Regulations: Good Clinical Practice and Clinical Trials
Report Problems to FDA
Complaints relating to Clinical
Regulations: Good Clinical Practice and Clinical Trials
SHARE
TWEET
LINKEDIN
PIN IT
EMAIL
PRINT
FDA Regulations Relating to Good Clinical Practice and Clinical Trials
Preambles to GCP Regulations
FDA Regulations Relating to Good Clinical Practice and Clinical Trials
Sign up for Good Clinical Practice/Human Subject Protection e-mail updates
FDA regulations governing the conduct of clinical trials describe good clinical practices (GCPs) for studies with both human and non-human animal subjects

ICH GCP

- Good Clinical Practice (GCP): international ethical and scientific quality standard
- Established in 1990
- Maintained by International Council for Harmonisation (ICH)
- Founding Members: European Union, Japan, USA

ICH
harmonisation for better health

Good Clinical Practice (GCP)

- The first version of the ICH E6 Good Clinical Practice (GCP) Guideline was finalized in 1996.

- Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Good Clinical Practice (GCP)

- The guideline was amended in 2016 to…
  - encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and
  - Updates standards re: electronic records and essential documents intended to increase clinical trial quality and efficiency

ICH Guidelines

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

ICH GCP: E6

Ethics

1. … conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP and applicable regulatory requirements
2. Before trial, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual subject and society. Anticipated benefits must justify risks.
3. Rights, safety, and well-being of subjects prevail over interests of science and society

ICH GCP: E6 *(continued…)*

Protocol and Science

4. Nonclinical and clinical information supports the proposed trial

5. Trials should be scientifically sound and described in a clear detailed protocol

ICH GCP: E6 *(continued…)*

Responsibilities

6. IRB approval prior to initiation

7. Medical care/decisions on behalf of subject made by qualified physician/dentist

8. Each individual is qualified (education, training, experience) to perform his/her tasks

ICH GCP: E6 *(continued…)*

Informed Consent

9. Freely given from every subject prior to participation

Data Quality and Integrity

10. All trial data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
11. Protects confidentiality of records

ICH GCP: E6 *(continued…)*

Investigational Products

12. Manufacture, handling, storage should conform to Good Manufacturing Practice (GMPs) and used per protocol

Quality Control/Quality Assurance

12. Implementation of systems with procedures to ensure quality of every aspect of the trial

So many protocol standards…

- **Regulations (OHRP, FDA**, HIPAA)
- **Guidance/guidelines (NIH, FDA, ICH GCP)**
- Government sponsor (i.e. NIH Institute/center-specific policies)
- Industry sponsor policies
- Other Institution policies (e.g. when other institution is sponsor)
- State/local laws
- Institutional/departmental policies
  - **IRB policies (see BUMC/BMC HRPP Procedures & Policies)**
  - **IRB policies (see UVM RPO Procedures & Policies)**

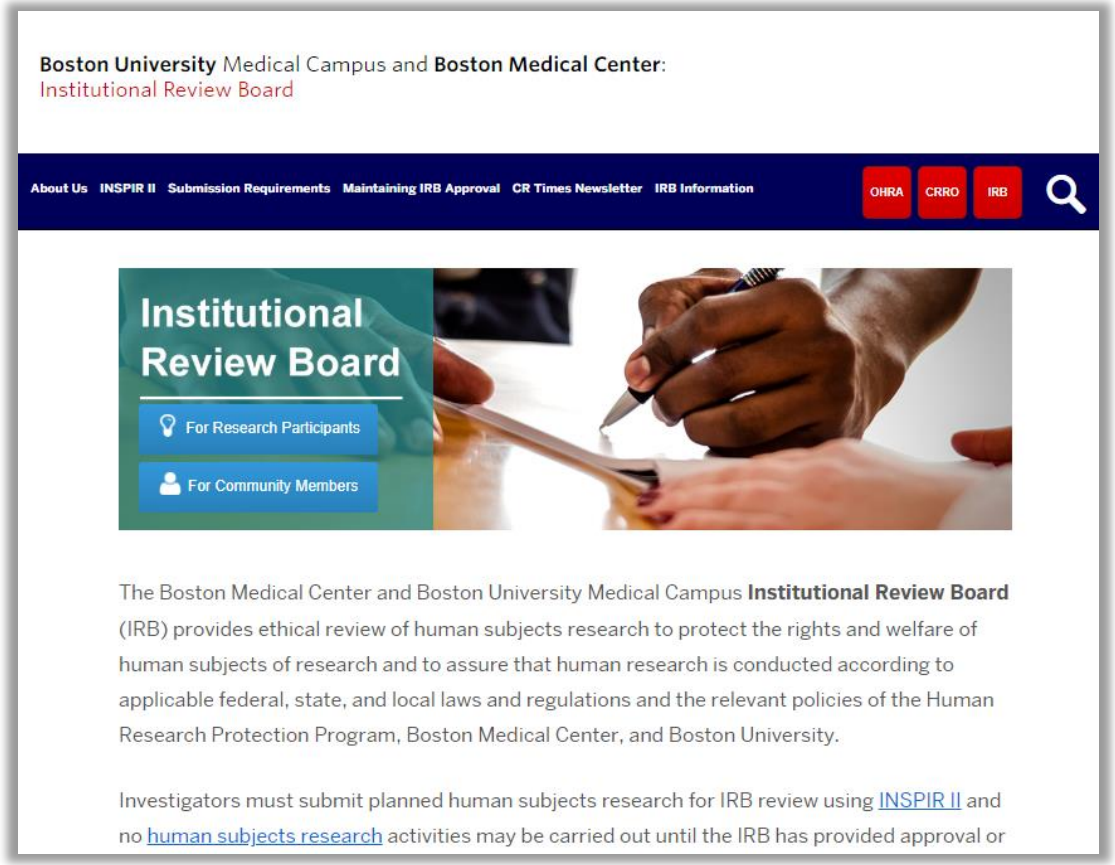
- **ICH Good Clinical Practice (GCP)**

Seems like a lot right?

There is an organization that is very close to home and here to assist…

Institutional Review Board

Institutional Review Board (IRB)



www.bumc.bu.edu/irb/

www.uvm.edu/rpo/human-subjects-research

Institutional Review Board (IRB)

- Formally designated committee; at least 5 members
  - Function as an ethics committee;
  - Primary responsibility: protect rights and welfare of research subjects
- Review, approve, conduct periodic review (at least annually) of biomedical and behavioral research [protocols]
  - Document that reviews take place in compliance with regulations
- Empowered to approve, require modifications or disapprove research protocols

- **The IRB enforces the rules of other organizations**

The 111 Criteria

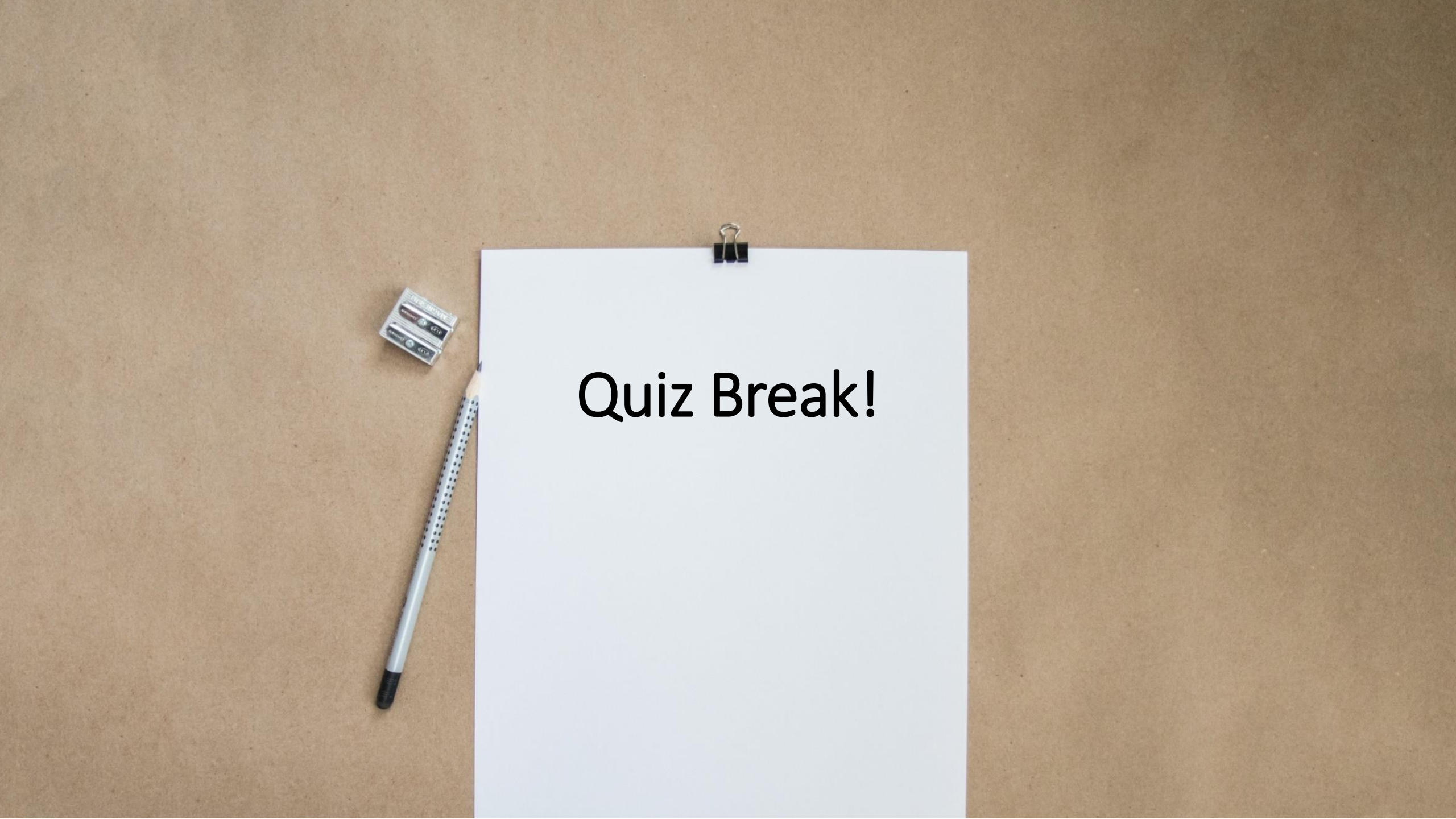
- The IRB reviews your protocol to ensure that it meets the 111 criteria from the FDA and OHRP

- Criteria are common to the FDA & OHRP

- Why “111”?
    - FDA: 21 CFR 56.111
    - HHS/OHRP: 45 CFR 46.111

The 111 Criteria

1. Risks to subjects are minimized.
2. Risks to subjects reasonable in relation to benefits.
3. Selection of subjects is equitable.
4. Informed consent process.
5. Informed consent documentation.
6. Adequate provision for monitoring the data.
7. Provisions to protect privacy/maintain confidentiality.
8. Safeguards for vulnerable populations.


Quiz Break!

RPN Workshop: Protocol Compliance Quiz

Please complete the quiz prior to the start of today's presentation. We will learn the answers as we go!

1) In what year did the International Conference on Harmonisation (ICH) establish Good Clinical Practice standards for conducting trials?
    a. 1914
    b. 1948
    c. 1979
    d. 1996

2) Under which category do the ICH GCP guidelines fall?
    a. Quality
    b. Safety
    c. Efficacy
    d. Multidisciplinary

3) What is the primary role of the Institutional Review Board?
    a. To regulate any research involving human subjects conducted or supported by and Federal department or agency
    b. To enforce the rules of other organizations that are related to the design and conduct of research
    c. To regulate any experiment that involves a test article and one of more human subjects
    d. To keep PIs and their research staff on their toes

4) The 111 Criteria are… (select all true statements)
    a. …named for their common regulation number.
    b. …the 111 principles established by the Office for Human Research Protections for conducting trials with human subjects.
    c. …the number of GCP considered during the first meeting of the International Conference on Harmonisation.
    d. …criteria for IRB approval of research.

5) Which of the following should be minimized or eliminated in the design of research study?
    a. Confidentiality
    b. Compensation to participants
    c. Risks to subjects
    d. All of the above

Dr. Ruth proposes to conduct research in which she will interview men who have self-identified as having experienced cognitive decline in the last 5 years. The aim of the research is to determine whether the men carry a genomic biomarker that indicates an increased risk for Alzheimer's Disease. Dr. Ruth's recruitment plan involves research assistants putting up posters in the surrounding community. The posters instruct any interested men, ages 45-65 and who have experienced difficulties with memory, to call the lab phone number and leave a message with their name and phone numbers. A member of the research team will return their call with available times to complete the study screening by phone. The team member will leave at least five different times to facilitate subjects' ability to participate. If the man meets eligibility criteria and is still interested in participating, the research team member will schedule an appointment at the lab where they would complete the consent process and the interview.

Yes, the research protocol minimizes potential risk of harm to participants in the recruitment process.

No, the research protocol does not minimize potential risk of harm to participants in the recruitment process.

Why is protocol compliance important?

a) Participant safety

b) Integrity of the science

How does protocol compliance address participant safety?

111 Criteria #1

1: Risks to subjects are minimized:

(i) Protocol should be using procedures that are consistent with sound research design and do not unnecessarily expose subjects to risk,

(ii) and whenever appropriate, **protocols should be using procedures that already being performed on the subjects for diagnostic or treatment purposes**

How does protocol compliance address integrity of science?

- Consistency of data collection *(protocol adherence, IRB oversight)*
- Ensuring staff are educated and trained for their roles *(ICH GCP E6, #8)*

Let’s revisit our definition…

- Compliance is…adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

- The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment,…

- ….except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

How do you change a protocol?

- **Amendment:** Making a change to the overall protocol
- **Exception:** A request of a one-time change to the protocol <u>prospectively</u> without actually altering the overall protocol

In the moment changes?

Let’s revisit our definition…

- Compliance is…adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

- The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment,…

- ….except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

Unplanned changes

- "….except where necessary to eliminate an immediate hazard(s) to trial subjects,"

- What situations meet this criteria?

Demonstrating Compliance

- If comply with your protocol, but you do not document it, did it really happen?...

  - Documentation is a requirement of numerous regulations!
    - 45 CFR 46 – OHRP Common Rule
    - 21 CFR 312.62(b) - FDA
    - ICH GCP E6, part 8

Demonstrating Compliance: Best Practices

Document Participant Eligibility

Document Consent

Document Data

Document Contacts (calls, study visits, etc.)

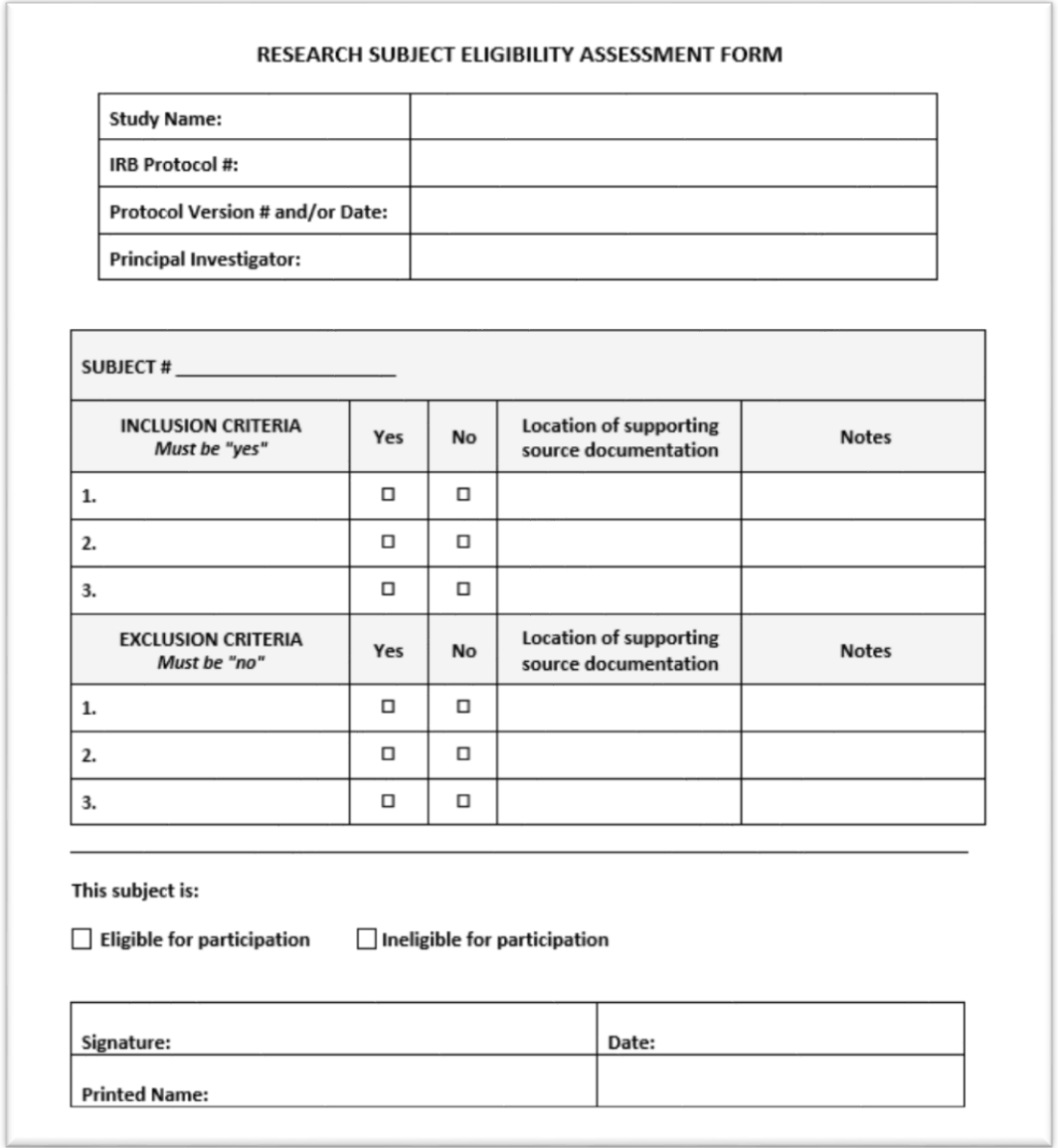
Document protocol changes!

Demonstrating Compliance: Best Practices

Document

Participant

Eligibility



RESEARCH SUBJECT ELIGIBILITY ASSESSMENT FORM

Study Name:	
IRB Protocol #:	
Protocol Version # and/or Date:	
Principal Investigator:	

SUBJECT # _____

INCLUSION CRITERIA *Must be "yes"*	Yes	No	Location of supporting source documentation	Notes
1.	☐	☐		
2.	☐	☐		
3.	☐	☐		
EXCLUSION CRITERIA *Must be "no"*	**Yes**	**No**	**Location of supporting source documentation**	**Notes**
1.	☐	☐		
2.	☐	☐		
3.	☐	☐		

This subject is:

☐ Eligible for participation ☐ Ineligible for participation

Signature:	Date:
Printed Name:	

Demonstrating Compliance: Best Practices

Document Consent

BOSTON MEDICAL CENTER AND THE
BOSTON UNIVERSITY SCHOOLS OF MEDICINE,
PUBLIC HEALTH AND DENTAL MEDICINE

BOSTON MEDICAL
EXCEPTIONAL CARE. WITHOUT EXCEPTION

RESEARCH CONSENT FORM

Basic Information

Title of Project: Evaluation of Stress Indicators on the Kree Population

IRB Number: H-12345

Sponsor: National Institute on Aging (NIA)

Principal Investigator: Carol Danvers, MD
100 Avenger Circle
Hudson River Valley, NY 12429
captainm@bu.edu

Study Phone Number: 212-576-4000

Study Name: Study PI:
Study IRB #:

Documentation of Informed Consent

Participant:	
Version of consent used:	
Consent obtained by:	
Date of consent:	

Check all that apply (provide necessary details in the notes space below):

- ☐ The consent form was signed and dated by the researcher.
- ☐ The consent process was witnessed by an impartial witness (if applicable).
- ☐ The participant was given a copy of the signed informed consent form.
- ☐ The consent process was completed *prior to the start of research procedures.*

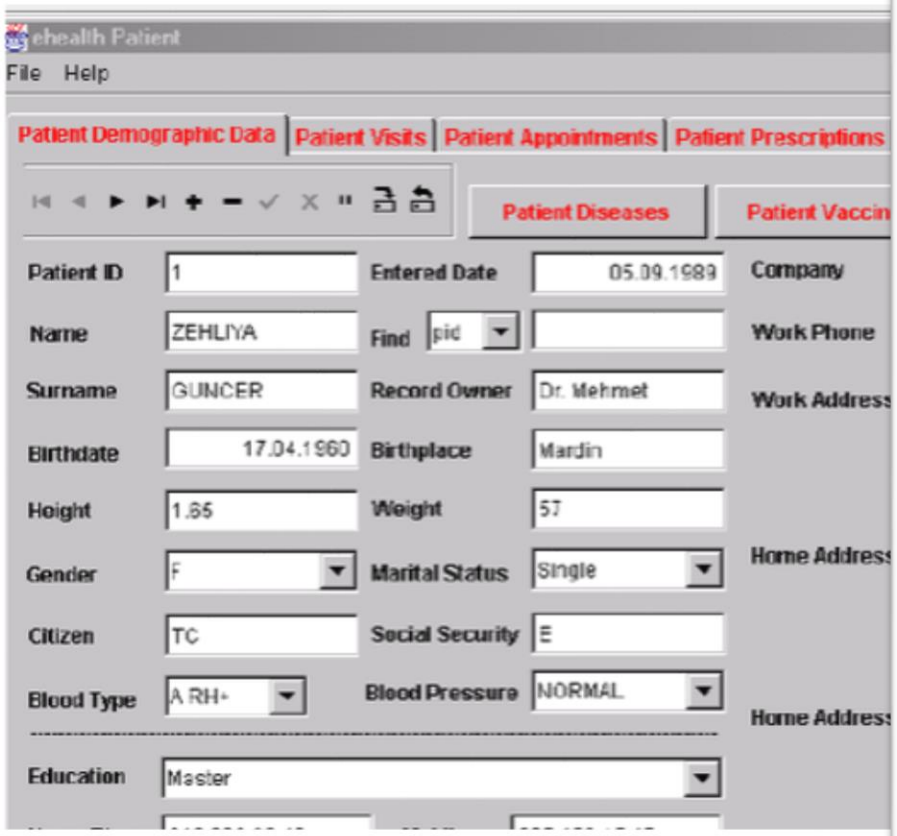
Notes about the consent process (i.e. who was involved in consent process, what questions did the participant have, translator number, whether a teach-back process was used, etc.):

_____

_____

Demonstrating Compliance: Best Practices

Document Contacts (calls, study visits, etc.)



Study name: **Study PI:**
Study ID #:

Phone Call Summary Report

For documentation of phone calls related to the clinical conduct of the study. You may also use Communication log template to document phone calls.

Date: **/ Time:**
Contact Person:
Contact Person Phone #:
Contact Person Institution:

Summary:

Demonstrating Compliance: Best Practices

Document protocol changes

Study name:
Study ID #:

Study PI:

IRB Submission Tracking Log

This log tracks submissions to the IRB, specifically initial protocol submissions, amendments and progress reports. Separate tracking logs may be used for tracking of AE/UP submissions and submissions of deviations and exceptions. Maintaining such a log helps the site to view the current status and history of changes made to the protocol.

Item(s) submitted (if amendment, briefly describe)	Submission Date	Approval Date	Comments

Demonstrating Compliance: Best Practices

Can you think of any other processes in your research study that could be documented?

Demonstrating Compliance: Best Practices

Possible Answer: Document training of staff!

Study Name:
Study IRB #:

Study PI:

Staff Member Training Log

This log documents training of individual staff members. To record specific training for an entire group (if easier) refer to "Staff Training Log for Groups."

Study Staff Member Name:

Date of Training	Name and/or Description of Training (include trainer name, if applicable)	Expiration date (if applicable)	Staff Initials	Trainer Initials (if applicable)

So what happens when we do not follow the protocol…

- Deviations
  - Definitions
  - Reporting (e.g. RENIs)
  - Resolving (e.g. CAPAs)
  - Tracking your follow-up (be prepared to demonstrate that you have followed your CAPAs)

Deviations

- Any change implemented without receiving IRB approval first
- Major deviation: Deviations that could affect the subject safety or integrity of the data
- Minor deviation: Deviations that are not major
- Each type has a separate requirement of when they should be reported to your IRB. This is outlined in your IRB's policies (or the external IRB that your may study follow!)

So what happens when we do not follow the protocol…

- Deviations
  - Definitions
  - **Reporting (e.g. RENIs)**
  - **Resolving (e.g. CAPAs)**
  - **Tracking your follow-up (be prepared to demonstrate that you have followed your CAPAs)**

  - **The RPN had workshops in the past to discuss RENIs, CAPAs, etc. in more details so feel free to look these up online!**

Questions?

Bonus Question:

You are conducting a NIH-funded study that will enroll subjects that have been prescribed an FDA-approved medication (Zocor) for the treatment of high cholesterol as part of their routine care Study participation will involve EKG, EEG, exercise testing, blood sampling (~30ml), survey completion and the collection of information from the medical record every 6 months. The study has been actively enrolling subjects for the past 2 years and you've just received a notification that the study will undergo a routine QA review by HRPP**. Under which of the following regulations and/or guidelines will the study be reviewed:**

a) FDA regs
b) OHRP regs
c) IRB protocol
d) Zocor Co. regs
e) a & c
f) b & c
g) c & d

Thank you!

Keep a look out for future RPN workshops…

Thank you!

Michelle St. Paul, M.A.

Special Projects & IRB Manager

mstpaul@bu.edu

Extra slides…

Demonstrating Compliance: Best Practices

Answer: Document training of staff!

Study Name:
Study IRB #:

Study PI:

Staff Member Training Log

This log documents training of individual staff members. To record specific training for an entire group (if easier) refer to "Staff Training Log for Groups."

Study Staff Member Name:

Date of Training	Name and/or Description of Training (include trainer name, if applicable)	Expiration date (if applicable)	Staff Initials	Trainer Initials (if applicable)

. Applicable Regulations, Guidances and Policies

Regulation/ Guidance/Policy	Title
21 CFR 50	Protection of Human Subjects
21 CFR 56	Institutional Review Boards
21 CFR 312	Investigational New Drug Application
21 CFR 812	Investigational Device Exemptions
45 CFR 46	Protection of Human Subjects
45 CFR 160	HIPAA Privacy Rule
45 CFR 164 Subparts A and E	HIPAA Privacy Rule