Research Ethics, Human Research Protections and Institutional Review Boards

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March 29, 2024

Agenda

History of Misconduct in Research

Guidelines/Principles

Federal Regulations

Definitions

Institutional Review Board

Types of Studies

CWRU IRB Protocol Submission

Approved IRB Protocol

History of Misconduct in Research

History of Misconduct in Research

- 1932-1972: Public Health Service Untreated Syphilis Study
- 1942-1945: Nazi Experiments (WWII)
- 1962: The Thalidomide Tragedy
- 1963: The Milgram Study
- 1963: Willowbrook Study

USPHS- Untreated Syphilis: 1932-1972

- Observation of natural course of disease
- Informed Consent was not obtained
- Being treated for “bad blood”
- In exchange:
  - Free medical exams
  - Free meals
  - Free burial insurance

USPHS- Untreated Syphilis: 1940's

- Penicillin safe/effective treatment
- Denied treatment & study continued
- 1972
- Tuskegee Health Benefit Program
- 1975

What is Common Thread?

“The participant did not freely and knowingly volunteer for the research because pertinent information was withheld that, if known, would have compelled a refusal to participate in the study.”

History

PRINCIPLES / GUIDELINES

- **1947: Nuremburg Code**
- **1964: Declaration of Helsinki (WMA)**
- **1979: Belmont Report (National Committee) (autonomy, beneficence, justice)**
- 1990: ICH Guidelines / "GCP"
- 1995-01: National Bioethics Advisory Committee
- 1990: National Committee for QA (VA)
- 2001-06: President Council on Bioethics
- *2001: Association for Accreditation of Human Research Protection Program (AAHRPP)*
- 2006: Secretary Advisory Comm. on Human Research Protections (SACHRP)

REGULATIONS

1966: NIH requires IRB approval
1981: CFR 45, Part 46
1986: CFR 21, Part 50

2000: HIPAA

2019: Revised Common Rule

Historical Background

- World War II turning point in establishment of national and international guidelines
- Many guidelines have been developed
- Some provide broad standards, others specific to research on diseases (e.g.; WHO guidelines for HIV AIDS)

Nuremberg Code

1947

Nuremburg Code

- The voluntary consent of the human subject is “absolutely essential” - research subjects should have legal capacity to consent

- Research subjects “should be so situated as to be able to exercise free power of choice”

Principles of Nuremburg Code

- Informed consent should be **obtained without coercion**
- **Qualified scientists** should conduct research
- Physical and mental suffering and injury must be avoided
- **No expectation of death or disabling injury**

Declaration of Helsinki

1964 and revisions 2013

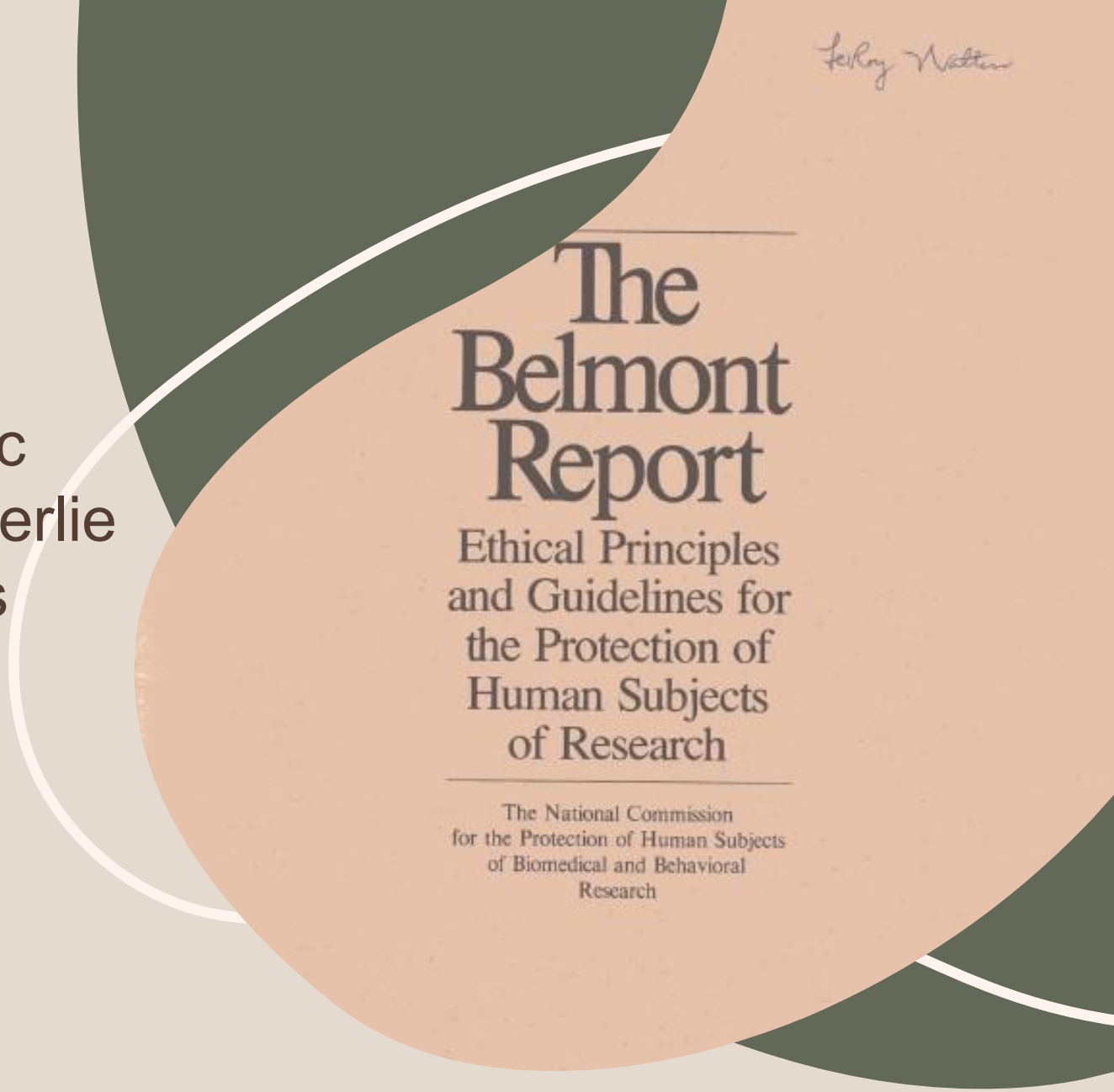
Declaration of Helsinki

- **World Medical Association (WMA)**
- Modeled on **Nuremberg Code**
- **Requires** qualified investigators, and consent of subjects
- *1975 revision* recommend review of research by an independent committee

Belmont Report 1979

Bioethics Commission

- Charged with identifying the basic ethical principles that should underlie research with human participants
- Summarizes the basic ethical principles identified by the Commission



Ethical Principles of Belmont Report

Ethical Framework- Belmont Report

Belmont Report (Principles):		Federal Regulations:
Respect for Persons	→	Informed Consent
Beneficence	→	Assessment of Benefits and Risks
Justice	→	Selection of Subjects

United States Federal Regulations for Human Research

Common Rule

45 CFR 46

1981

Common Rule- 45 CFR 46

Part A- IRBs, Institutions and Researchers

Part B- Pregnant women, human fetuses, and neonates

Part C- Prisoners

Part D- Children

Changes to Common Rule- 45 CFR 46

- Expansion of exempt categories, emphasis on low risk
- Eliminate continuing review requirement for studies that undergo expedited review
- US institutions, collaborative research, only one IRB

Definitions

“Research”

- Systematic investigation
  (includes research development, testing and evaluation)

- Designed to develop or contribute to generalizable knowledge

“Human Subject” (OHRP)

- Living individual
- About whom an investigator conducting research obtains **either**:
  - Data through intervention or interaction with the individual **OR**
  - Identifiable private information

“Risk” (OHRP)

- Probability of harm or injury occurring as a result of participation in a research study

- Risk can include:
  - Physical
  - Psychological
  - Social
  - Economic

OHRP- Defining Minimal Risk: 46.102(i)

"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Institutional Review Board: IRB

Institutional Review Board (IRB)

- Independent group
- Charged with reviewing research
- Ensure that human subjects' rights and welfare are adequately protected

IRB's Purpose & Responsibilities

- Federal Regulations
- Protect human subjects (harm)
- Support and facilitate the ethical conduct of human research (rights & integrity)
- Assure institutional compliance with regulatory agencies
- Assist investigators in complying with the ethical and regulatory standards

Criteria for IRB Approval

- Risks Minimized
- Risk-Benefit Ratio Reasonable
- Equitable Selection of Subjects
- Privacy / Confidentiality
- Data Safety Monitoring
- Informed Consent Sought
- Informed Consent Documented
- Additional Protections for “Vulnerable Populations”

Belmont Report

- Respect for Persons

- Beneficence
  - Maximize benefits and minimize harms
  - Importance of good methodology- yield benefits to society

- Justice

Risks are Minimized

- Procedures are consistent with sound research design and subjects are not exposed to unnecessary risks

- Use procedures already being performed on subjects for diagnostic or treatment purposes

Belmont Report

- Respect for Persons
- Beneficence
- Justice
  - Moral requirements- fair procedures and outcomes in the selection of research participants
  - Equitable distribution of burden of research and anticipated benefits
  - Who is likely to benefit from the outcomes

Justice

Ensuring fair and equal administration of non-exploitative and well-considered procedures to potential research participants

Justice

- Moral requirements- fair procedures and outcomes in the selection of research participants
- Equitable distribution of burden of research and anticipated benefits
- Who is likely to benefit from the outcomes?

Equitable Subject Selection

- Equitable Selection does not mean that all groups are represented in proportion to the population
- Selection criteria should be both fair and appropriate to the research question
- No group should be unduly burdened or will unfairly benefit from the research

Equitable Selection of Subjects

- Age
- Economic Standing
- Ethnicity
- Gender
- Language
- Literacy
- Race

Belmont Report

- Respect for Persons
  - Self-determination
  - Decision making
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- Beneficence
- Justice

Respect for Persons

There are three considerations:

- Protecting the autonomy of a patient
  (the ability to make decisions voluntarily without coercion)
- Protecting patients with diminished autonomy
  (e.g.; mental disorders, children, extremely ill)
- Being truthful and conduct no deception

Informed Consent Process

Purpose:

To ensure knowledgeable decision making and voluntary participation

Informed Consent

Informed consent process involves:

- Providing adequate information
- Providing other options
- Providing the opportunity to withdraw
- Ensuring full comprehension by the participant
- Responding to questions
- Obtaining voluntary participation

Key Information Section

1. Purpose of the research
2. Major study activities in lay terms, and expected duration of participation
3. Primary reason a person might want to participate (benefits)
4. Primary reason a person might not want to participate (risks)
5. Please refer to the Detailed Consent for additional information

Eight Basic Elements of Consent

1. Statement that the study is research
2. List of risks or discomforts
3. Any benefits
4. Information on how the research data will be kept confidential
5. If there is additional risk in participating in the study, what other options a person might have

Eight Basic Elements- continued

6. Contact information for someone a participant can contact is they have questions or concerns
7. Statement that participating in the study is completely voluntary
8. When identifiable information is collected, there must be a statement regarding any use of the information in the future

Additional Information (as applicable)

- Risks that are currently unforeseeable
- Termination of participation
- Withdrawal
- New findings which might impact participation
- Number of participants
- Commercial profit from biospecimens
- Incidental findings

Compensation

- **[If there are no costs to the subject:]** There will be no costs to you for study participation.
- ***[If there is a cost, please delete the previous sentence and explain the cost to subjects.]***

- ***[If subjects will not be compensated]***
- You will not be compensated for your participation in this research study.

- ***[If no reimbursement will be provided]***
- You will not be reimbursed for any out-of-pocket expenses, such as parking or transportation fees.

[If subjects will be compensated and/or reimbursed]

•You will receive the following compensation/reimbursement: ***[Insert amount of payment information, payment method (i.e., class credits, gift cards, parking fees, etc.), as well as when payment will occur. Add information if compensation will be altered or pro-rated if a subject chooses to withdraw.]***

For example:

- You will receive _____ for your participation in this study. ***[Example: a $5 gift card to a local merchant, or: you will be entered into a raffle to win 1 of 10 Amazon gift cards worth $100; chances of winning are approximately 1 in 100.]***

- You will receive _____ for each _____ you complete. ***[Example: you will receive $5 for each survey you complete]***. There are ***[Enter # and type of study components.]*** Total compensation for participation in this study is ***[Enter total compensation for completion of the study.]*** If you decide to withdraw from the study or are withdrawn by the research team, you will receive compensation for the visits that you have completed.

Submission Guidelines: Informed Consent Document

- Translating a complex scientific project into lay language can be difficult
- Must be presented in language subject can understand
- May be delivered using non-traditional formats, such as video, website, etc *(check specific IRB rules)*
- May be provided by “legally authorized representatives”

Readability

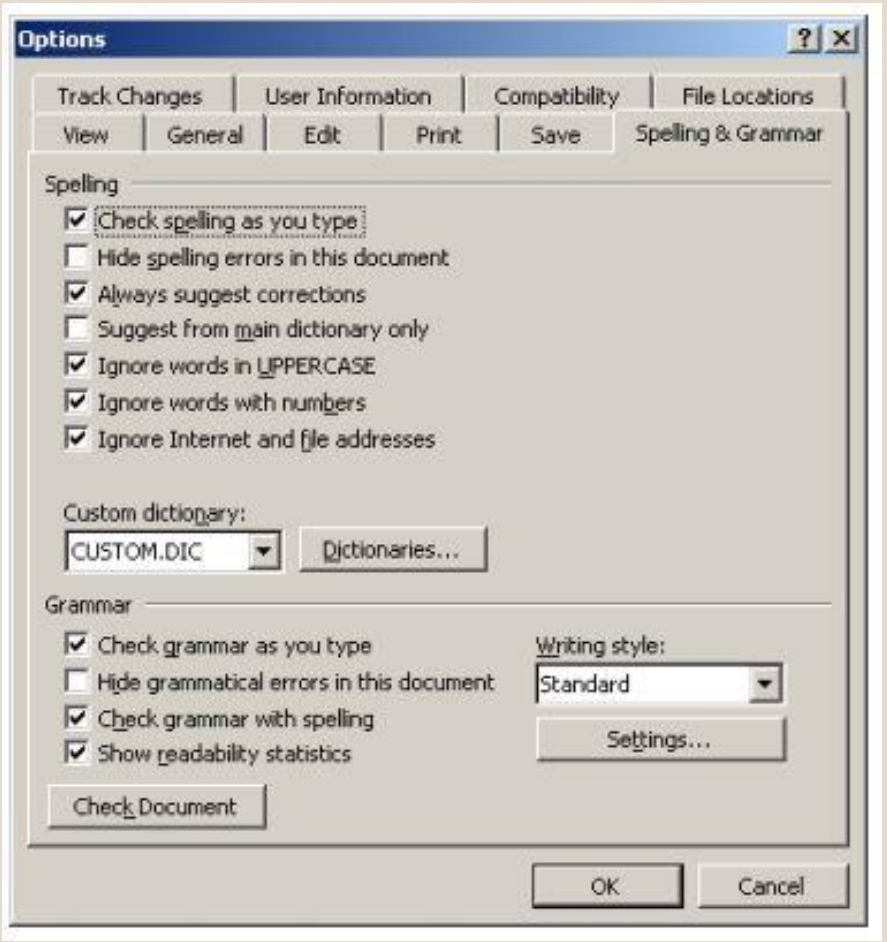
- Recommend an 8th grade reading level
- Use common, everyday words
- Write in second person, and use active voice

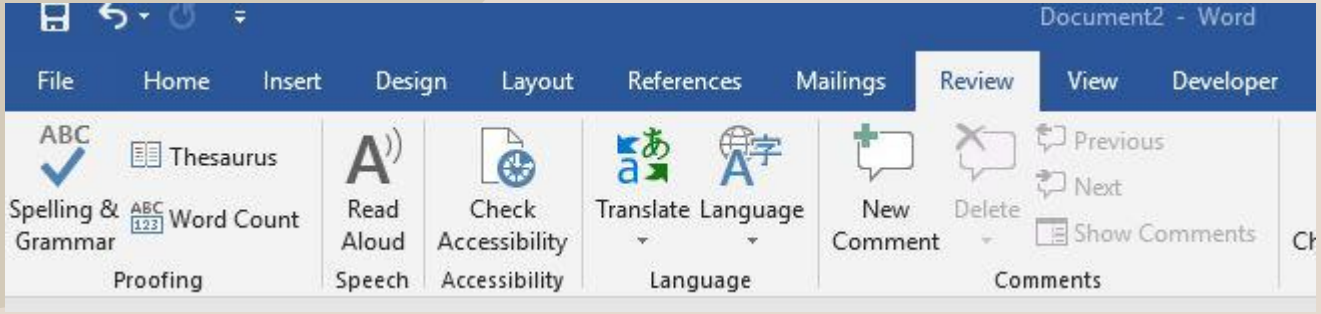
Instead of:

Use:

Readability

- Tools built into Word:
- Flesch-Kincaid Reading Level
- Flesch Reading Ease





ICD- Study Purpose

- *KEEP IT SIMPLE!*

- Examples:

"The purpose of this study is to investigate the cognitive-behavioral influences on medication adherence."

- *BETTER*:

"This is a research study to learn more about how people manage their illness and the medicines they take."

Visual Appealing

- Use pictures and/or graphics
- Help explain more complex procedures
- Make a document feel less intimidating
- Use of white space on page
- Headers
- Use of tables if the study involves multiple visits with different procedures

- *65% of the population are visual learners*

Submission Guidelines: Informed Consent Form

- May be waived altogether, with IRB permission
- May have attachments
- May need to be repeated over course of study, especially if cognitive abilities of subjects change or study data result in new relevant information
- Must disclose conflict of interests

Informed Consent Form (ICF)

As a part of the criteria for IRB approval (46.111(a)(4-5)), the IRB will need to verify that all the required elements of consent are present

(or appropriate justification has been given for a waiver).

Privacy

Privacy - Physical Surroundings

- Interviewing subjects in a public vs. private setting (waiting room vs. closed exam room)
- “The subject will fill out the questionnaire at their home or in a location of their choice.”

Confidentiality

Confidentiality - Tactics used to limit the risk that research DATA will be observed by anyone other than the researchers.

- Coding data
- Password protection
- Secure servers
- Locked file cabinets

Vulnerable Populations

Vulnerable Populations

Federally regulated protections

- Pregnant women, human fetuses and neonates- Subpart B
- Prisoners- Subpart C
- Children- Subpart D

Vulnerable- Special Populations

- Decisionally-impaired subjects
- Physically-challenged subjects
- Faculty Members
- University Students
- Employees

Vulnerable Populations:
children, students, acutely ill, cognitive impairment

- Limits to ability to protect self
- **Additional regulations**
- Justification
- Procedure for assessing capacity
- Extra measures to avoid coercion
- Surrogate consent
- Limits to acceptable risks
- Limits to acceptable compensation

Types of Research

When to apply for IRB Approval?

- Before conducting human research activities
- When applying for funding…
- Students

What Happens if Human Research is Conducted without IRB Approval?

- Common Rule- Regulations
  - Site the conduct of human research without IRB approval as Serious Non-compliance
- IRB Full Board makes determinations
- Impact on Conducting Research- Reportable Event

When unsure…

- Contact the IRB Office
- cwru-irb@case.edu
- IRB Website: Contact Information

Terminology- Always Ask!

- **Not human subjects:** Not intended to produce generalizable data (e.g.; QI, single case report)
  - Not involving living persons, or not involving any contact with living person and no identifying data
  - Research that uses publicly available data

- **Exempt Review Category:** research that uses anonymous or identifiable low-risk surveys, educational evaluations, etc

Exempt Review Category (continued)

Exempt with Limited Review: Ensure adequate Privacy and Confidentiality Safeguards for Identifiable Private Information:

#2: Surveys, Interviews, Educational Tests & Observation of Public Behavior

#3: Benign Behavioral Intervention

Terminology

- **Expedited Review Category:** Research that poses less than minimal risk, reviewed by IRB chair/vice-chair/ IRB member (e.g. record review, survey, non-invasive)

- **Full Board Review:** Research that is greater than minimal risk or does not fit in any of the Expedited Categories.

NIH Definition- Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Research vs Quality Improvement vs Case Study= Murky territory

Research: “Systematic collection of data for the purpose of producing generalizable knowledge”

Quality Improvement: Systematic collection of data for the purpose of improving performance of one specific entity

Case study: Report of 1 or 2 de-identified cases, for the purpose of illustration or learning

*All of these types of Research requires a “Determination” by the IRB

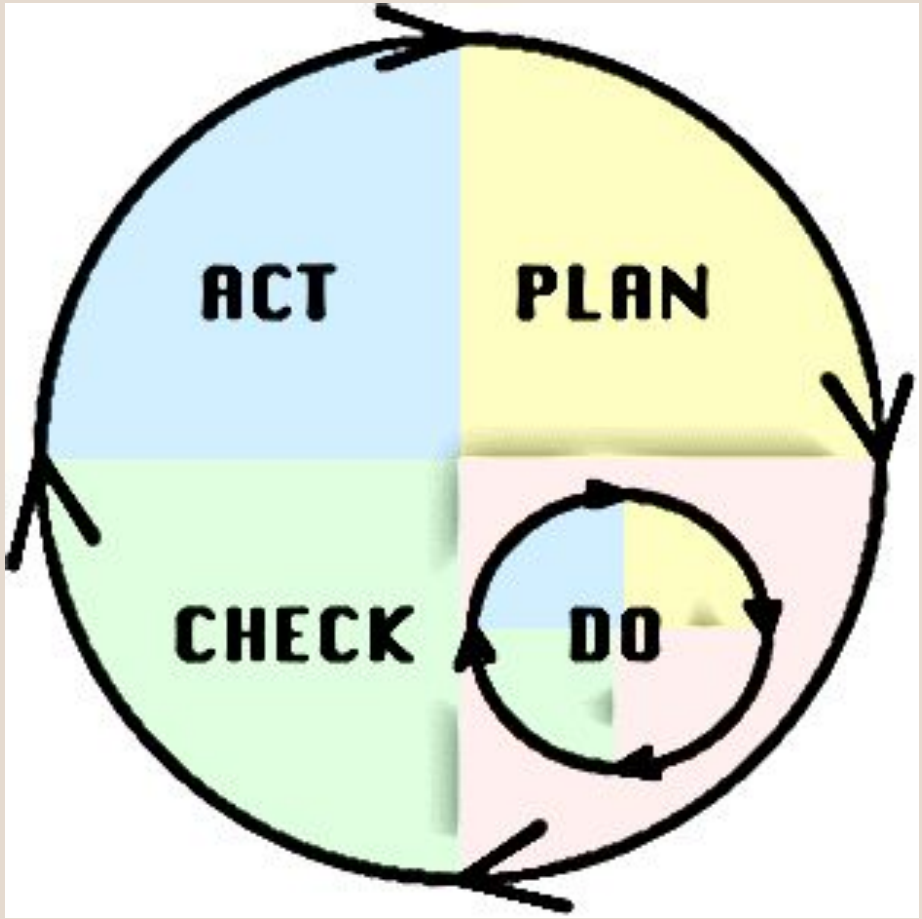
Important Questions to Ask

What are you trying to accomplish?

How will we know that a change is an improvement?

What changes can result in improvement?

Deming PDSA Model



Plan – Analyze and solve the problem

Do – Implement the solution

Study – Measure the change

Act – Modify as needed

Medical Records = PHI

If accessing medical records

-and-

No contact with participant:

- Waiver of Informed Consent
- Waiver of HIPAA authorization

Secondary Data Analysis

- Review of existing data for a specific purpose
- If data de-identified = consult IRB office

Conducting Research- Part of Larger Study

- Student dissertation
- Use of Data- Faculty Advisor Collected
- Recommendation- Consult with IRB Office

Difference between Data

- Anonymous
- De-identifiable
- Identifiable
- Restricted

Remote Data Collection

- Protocol should describe how you will be collecting data, and the remote platform being used.

- Be sure to follow current best practices issued by CWRU UTech for these remote platforms to ensure privacy and data security.

Remote Data Collection

Recommendations:

- For surveys: Qualtrics and CWRU REDCap
- For interviews: CWRU Zoom and phone

Identifiable Data

- Audio Recordings
- Video Recordings
- Zoom Recordings

Data Storage

- Privacy and confidentiality provisions remain critically important at all times, even when working remotely.

- Please note, collection, transmission, or access to private identifiable data or protected health information, must comply with university and other policies for security of research data.

Data Storage

- Remote interactions that will collect or transfer private identifiable information or protected health information should use technology that is IT secure or HIPAA compliant (e.g., CWRU REDCap, CWRU Box).
- Do not store private identifiable information or protected health information on unsecure devices in order to work remotely.
- Use University-approved BOX services and VPN access while working remotely instead of storing data directly on personal devices.

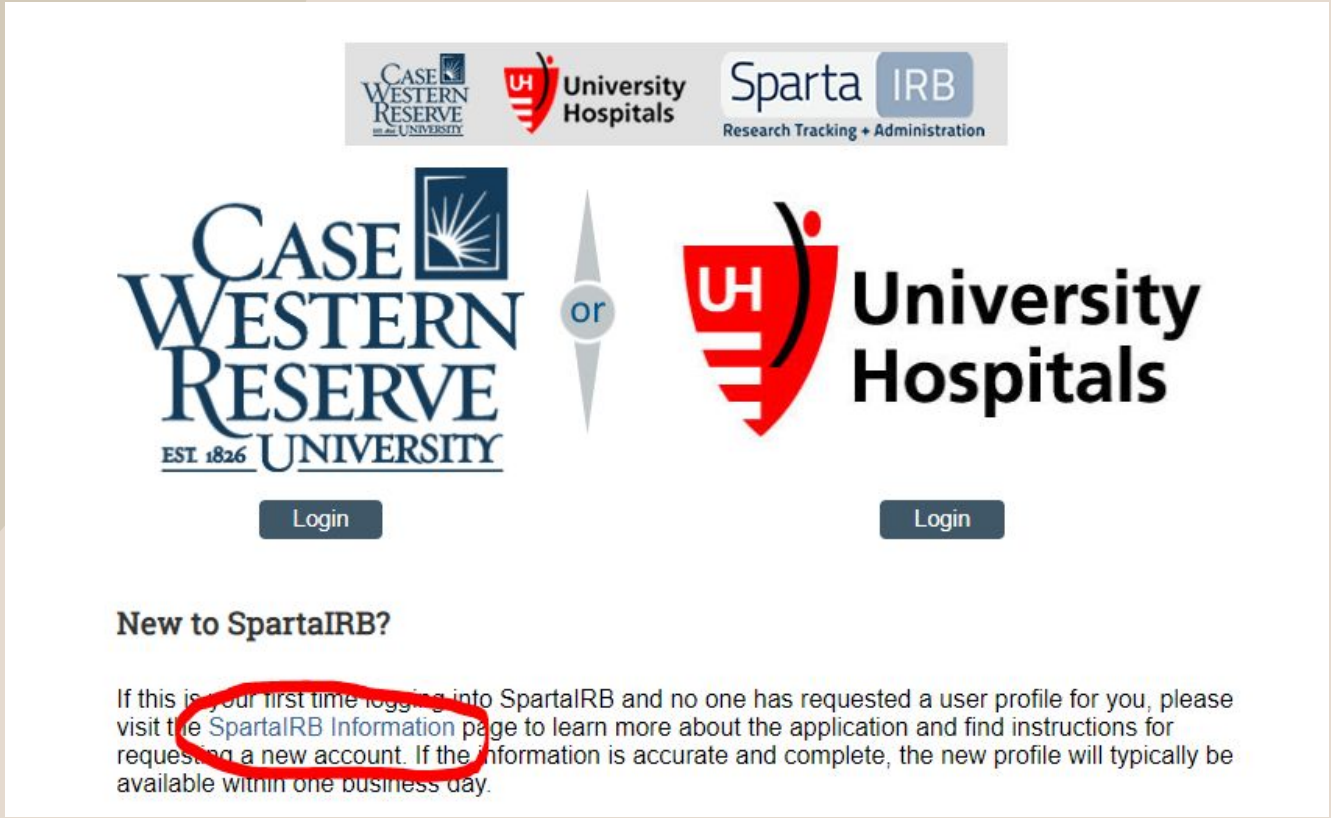
Submission Guidelines

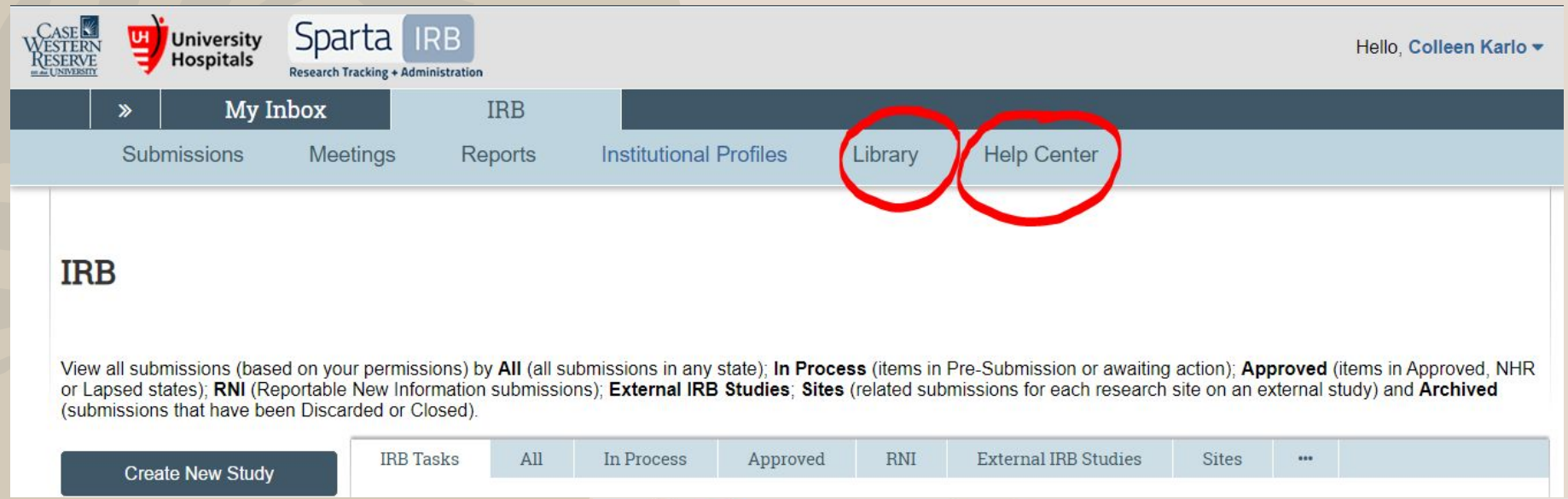
- Request for SpartIRB Account to be created
- Allow enough time
- Prepare the protocol
- Write the informed consent form (ICF)
- Obtain necessary approvals / support letters
- Submit electronically through the SpartaIRB system (User ID = Your Case ID)

Before Submitting Protocol Submission

- Access SpartaIRB
- Complete Smart form- Few questions that give overview of protocol
- Choose Protocol Template
- Required Chair/Departmental sign-off

SpartaIRB System

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University Hospitals
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Research Tracking + Administration
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My Inbox
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Submissions
Meetings
Reports
Institutional Profiles
Library
Help Center
IRB
View all submissions (based on your permissions) by All (all submissions in any state); In Process (items in Pre-Submission or awaiting action); Approved (items in Approved, NHR or Lapsed states); RNI (Reportable New Information submissions); External IRB Studies; Sites (related submissions for each research site on an external study) and Archived (submissions that have been Discarded or Closed).
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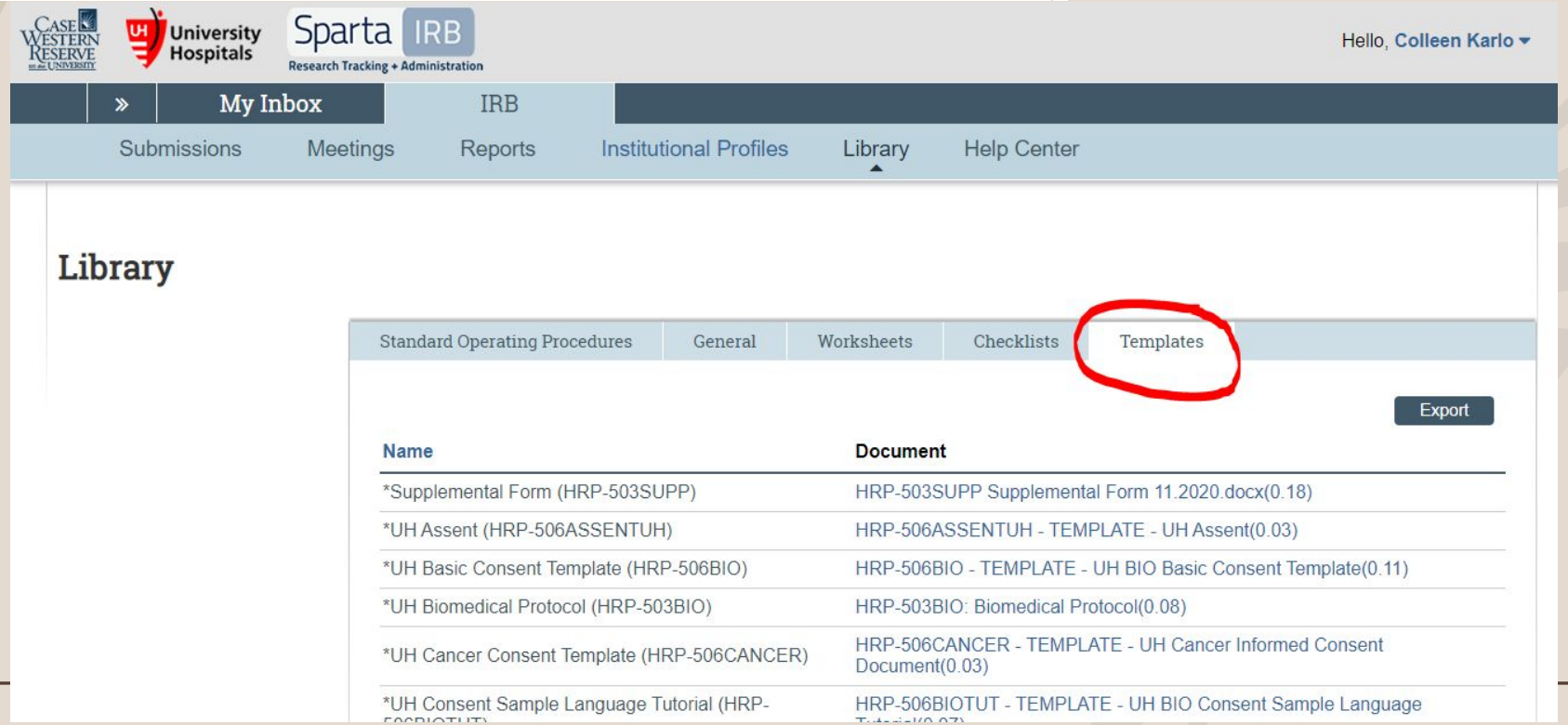
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*UH Assent (HRP-506ASSENTUH)
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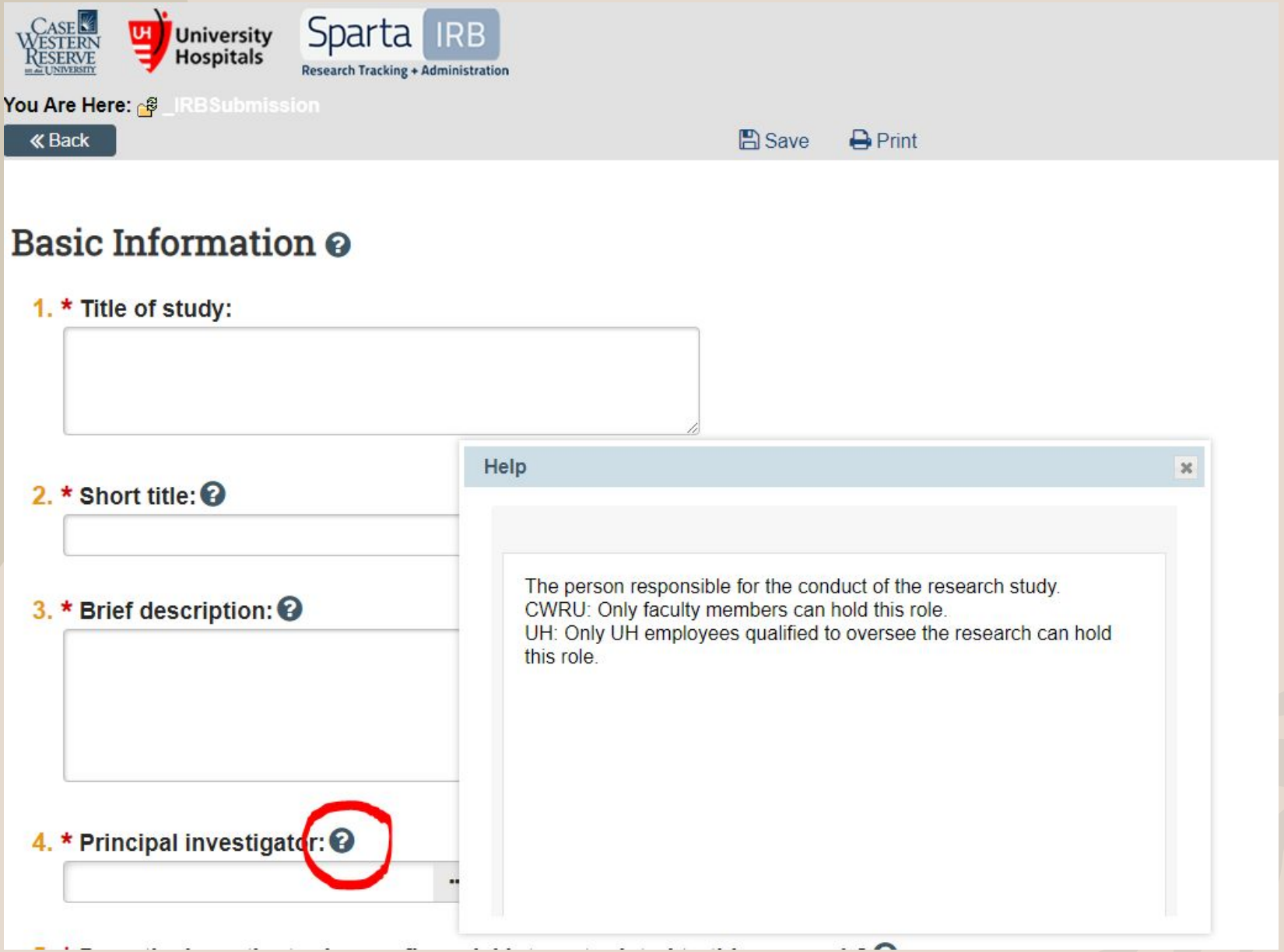
*UH Basic Consent Template (HRP-506BIO)
HRP-506BIO - TEMPLATE - UH BIO Basic Consent Template(0.11)
*UH Biomedical Protocol (HRP-503BIO)
HRP-503BIO: Biomedical Protocol(0.08)
*UH Cancer Consent Template (HRP-506CANCER)
HRP-506CANCER - TEMPLATE - UH Cancer Informed Consent Document(0.03)
*UH Consent Sample Language Tutorial (HRP-
HRP-506BIOTUT - TEMPLATE - UH BIO Consent Sample Language

Common Clarifications

- PI cannot be a student/resident
- Upload documents in correct sections
- Funding question must have an answer
- “Stack” Documents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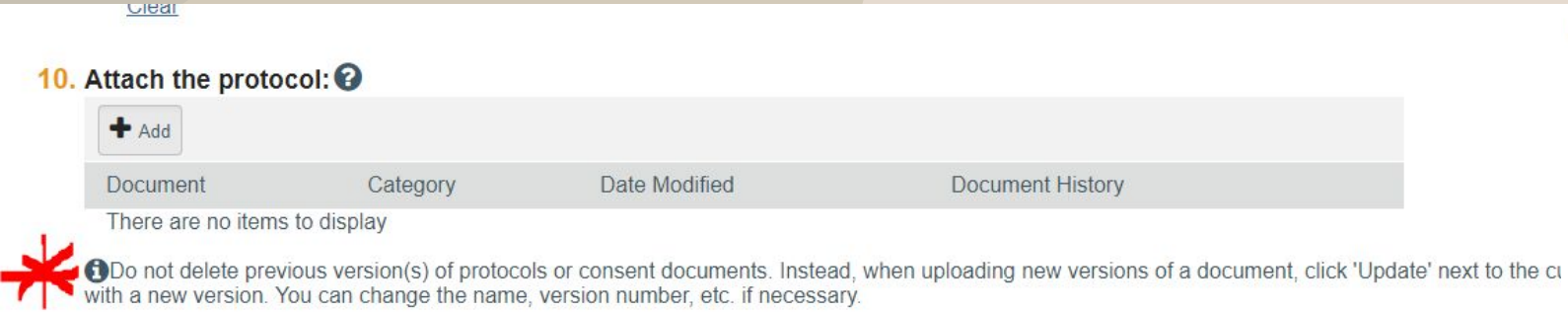
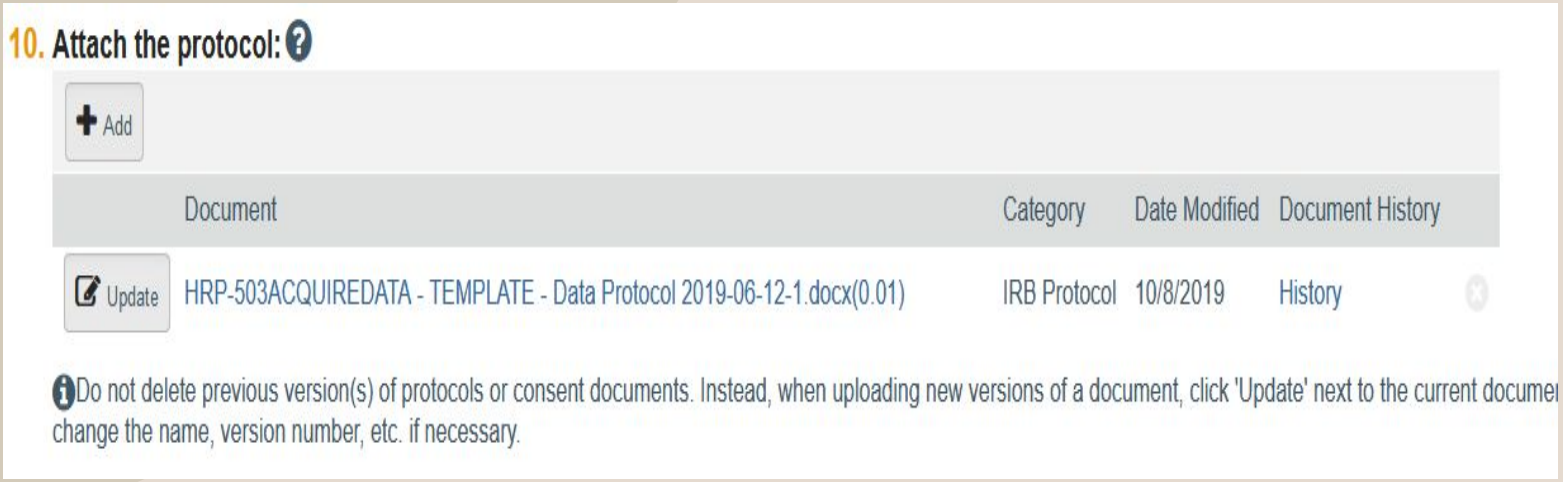
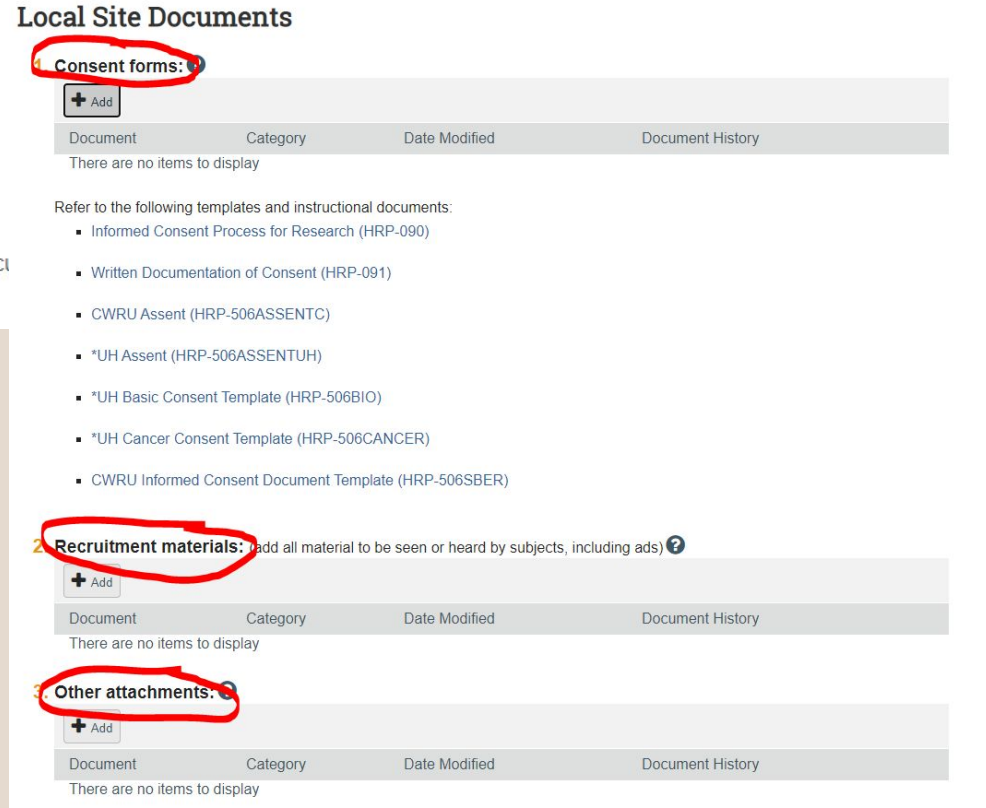
Print
Basic Information
1. * Title of study:
2. * Short title:
3. * Brief description:
4. * Principal investigator:
Help
The person responsible for the conduct of the research study.
CWRU: Only faculty members can hold this role.
UH: Only UH employees qualified to oversee the research can hold this role.

Uploading Documents in SpartaIRB







Additional Requirements

- The Continuing Research Education Credit Program (CREC) is CWRU's method of certifying that individuals are trained to conduct human research.
  - Complete Education *Requirements* https://case.edu/research/training/continuing-research-education-credit-crec-program
  - Submit Financial Conflict of Interest Disclosure https://case.edu/research/compliance/conflict-interests-committee

What else can help with IRB Process?

If you receive request for clarifications

- Do not send back to the IRB until all changes are made
- If you aren't sure, contact the IRB administrator
- All study members are required to:
  - Complete CREC Certification
  - Conflict of Interests Disclosure form will be required for faculty and may be required for staff/students on study team

Your IRB Protocol is Approved…

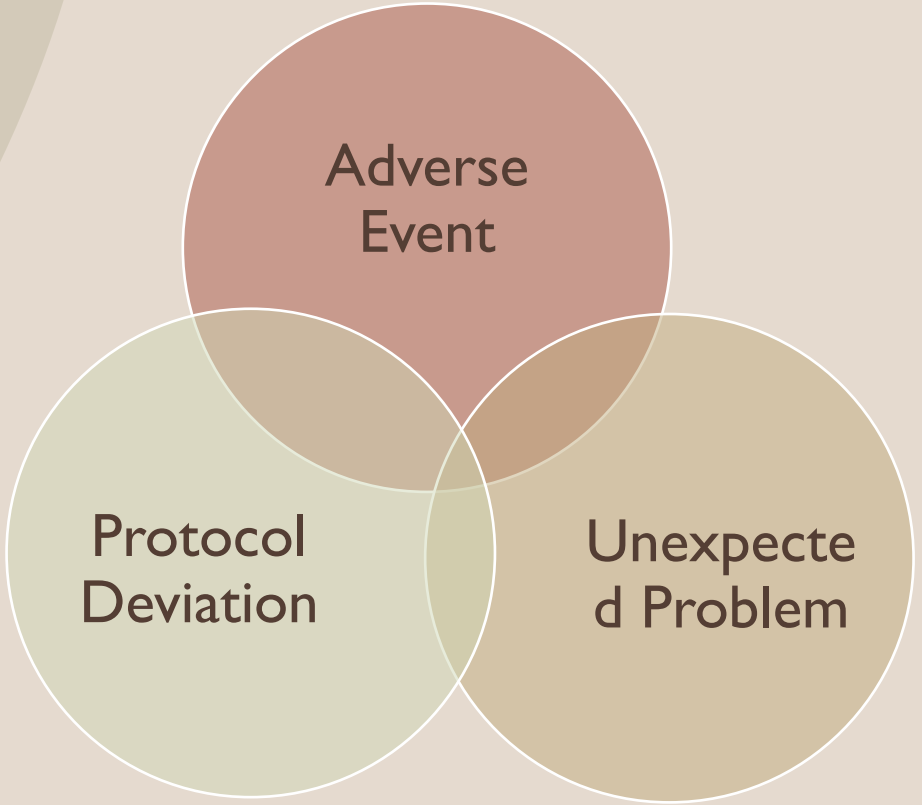
Now what?

Active Protocol Requirements

- Modification Requests
  - Submit prior to implementing any change
  - Currently active and exempt studies

- Continuing Review
  - Full Board IRB risk protocols
  - Special expedited review protocols

Adverse Event vs. Unexpected Problem vs. Protocol Deviation



EXAMPLES: Deviation vs. Problem vs Adverse Event

- Protocol Deviations: Altering ANY aspect
  - Change in timing of tests, follow-up
  - Violating enrollment criteria
  - Altering elements of the procedure

- Unexpected Problems:
  - Losing computer file
  - Sudden unavailability of drug, equipment

- Adverse events: Subject harm

Reportable New Information (RNI)

- Submitted via SpartaIRB System
- Method of How PI & Study Team Members Notify the CWRU IRB
- Section to Document Protocol Number

University Policy on Custody of Research Data

Faculty Handbook-

- Responsibilities & rights concerning
  - Access to
  - Use of
  - Maintenance of research data

- Responsible for maintenance & retention of research data

Retention of Data

Research data shall be archived for:

- Not less than three years after the final grant close-out /or/
- After publication resulting from the project
  - Whichever occurs last
  - Original data retained whenever possible

Additional Required Provisions

Participants Who Agreed to be Contacted for Future Research Studies

- Contact Information should be separate from the original Study Data

Once identifiable data (linked to individual participants)

- CWRU IRB Protocol can be closed

Resources for Tips to Destroy Data

- CWRU UTech Department = Great Resource
- Cal Frye- cxf244@case.edu

Student Research Studies

In the case of a student researcher, the PI may allow the student to take the original data (except for original informed consent documents if the study involves human subjects) when the student leaves the university as long as the student signs a written agreement (also signed by the PI and the Associate Vice President for Research or their designee) agreeing to accept custodial responsibilities for the data and that Case Western Reserve University will be given access to the data should that become necessary.

Summary

- IRB functions are mandated
- IRB office is good resource
- CWRU websites good resource
- Students should work with their advisor

- Ask when unsure

Guidance & Collaborations

- Steps to take when federal agencies regulations/guidelines are different
  - OHRP
  - NIH
  - FDA
- Secretory Advisory Committee for Human Research Protections (SACHRP)
- Continue to meet Data Sharing Policy

Any Comments, Questions or Concerns?

Contact the CWRU IRB

Email address:
cwru-irb@case.edu

Kim Volarcik
kav6@case.edu
216-369-0134