Fundamentals of Human Subject Protection and the IRB Process

Ensuring That All Research Involving Human Subjects Meets Federal, State, and Institutional Guidelines

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Learning Objectives

- Why Research is Regulated
- Guidelines and Regulations
- The Local IRB Process

The History

- The Tuskegee Syphilis Study
  - 1932 – 1972
- Nazi War Crimes of a Medical Nature
  - 1942 - 1946
- Willowbrook State School
  - 1956 – 1970s
- The Jewish Chronic Disease Study
  - 1963
**Tuskegee Syphilis Study**
- 1932-1972 U.S. Public Health Funded study to evaluate the natural history of untreated syphilis.
- 300 indigent, uneducated African American Sharecroppers with syphilis
- Thought they were receiving beneficial medical care
- 40 years of monitoring
- Denied cure even though it was available (Penicillin available in 1943)
- Results: 28 deaths, 100 disabled, 19 congenital syphilis births

**Nazi War Crimes of a Medical Nature**
- Gruesome experimentation on holocaust victims
- No consent or authorization
- Experiments had little or no scientific value
- Subjects not killed by experiments would be dissected and killed

**Willowbrook State School**
- 1950's Staten Island
- Vulnerable population: retarded children at extended care facility
- Deliberately infected with Hepatitis C
- Coercion: Parents were told that participation in the study was the only way their child could be admitted into the school
- "They are going to get it anyway"
Jewish Chronic Disease Study

- 1960’s, New York City
- Vulnerable population-senile, chronically ill patients
- Live cancer cells were injected into bloodstream
- Patients were not told
- Administration: “They are going to die anyway”

San Antonio Contraception Study

- 1970’s evaluate the effectiveness of female birth control pills.
- Indigent patients with no other place to go for advice or medication but the clinic.
- Randomized: active contraceptive or placebo.
- Women not informed.
- Results: High number of unplanned pregnancies in placebo group.

Guidelines & Ethical Considerations

Nuremberg Code (Required elements for using humans in research)
- Informed consent of the volunteers must be obtained without coercion of any form
- Research must be based on prior animal work
- Anticipated results should justify the experiments
- Only qualified scientists must conduct research
- Physical and mental suffering should be avoided
- There should be no expectation of death or disabling injury from any experiment
Guidelines & Ethical Considerations

Declaration of Helsinki
- Written in 1964 by the World Medical Association (portions updated in 2005)
- Reinterpreted the Nuremberg Code with a view toward medical research with therapeutic intent
- Set the stage for implementation of IRB process
  - Provided more specific guidelines
  - Duty to protect life, health, privacy and dignity
  - Emphasized subject understanding

Belmont Report 1979
U.S. Congress authorized the formation of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1974)
- Respect for Persons
  - Individuals should be treated as autonomous agents
  - Allow people to choose for themselves
  - Give extra protection to those who have limited ability or freedom to choose for themselves
  - Do not use people as a means to an end
- Beneficence (Do No Harm)
  - Maximize benefits
  - Minimize risks
- Justice
  - Treat people fairly
  - Fair sharing of burdens and benefits of research

Outcomes of the Belmont Report
- Beneficence (Do No harm)
  - Good research design
  - Competent investigators
  - Favorable risk-benefit analysis
- Respect for Persons
  - Informed consent
  - Respect for privacy (confidentiality-anonymous)
  - Right to withdraw
- Justice
  - Equitable selection of subjects
Federal Regulations

- Federal Policy adopted in 1981
  - Common Rule (1991)
- DHHS Regulations for the Protection of Research Subjects
  - 45 CFR 46, subpart A
    - Statement that the study involves research, explanation of purpose, duration of participation, description of procedures to be followed, identification of the procedure which is experimental.
    - Description of anticipated risks or discomforts to the subject.
    - Description of benefits to subjects or to others which may be expected.
    - Disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subjects.

Who is Covered?

- Dept. of Agriculture
- Dept. of Energy
- Dept. of Commerce
- Dept. of Justice
- Dept. of Defense
- Dept. of Education
- Dept. of VA Affairs
- Dept. Health and Human Services
- Dept. of Transportation
- NSF
- NASA
- EPA
- CIA

Responsibilities in Research

- Institutional Responsibilities
- Institutional Review Board Responsibilities
- Investigator Responsibilities
### Institutional Responsibilities

- **Federalwide Assurance**
  - Under Federal regulations, any institution engaged in Federally-supported human subjects research must commit itself in writing to the protection of those subjects.
  - UF guarantees adherence to Title 45, Part 46, of the Code of Federal Regulations.
  - UF will review ALL research involving human subjects.

### IRB Responsibilities

- **UF Utilizes 4 IRBs**
  - IRB01: Health Science Center
  - IRB02: Behavioral/Non-Medical
  - IRB03: Jacksonville
  - IRB04: Western IRB (Industry Sponsored)
- Review all proposed human subject research at the University of Florida in accordance with established guidelines.

### IRB Responsibilities Cont.

- Authority to approve, request modification in, and/or disapprove research.
- Authority to suspend or terminate previously approved research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects.
- To observe, or have a third party observe, the conduct of the research.
- To observe, or have a third party observe, the consent process.
Investigator Responsibilities

Investigators have the primary responsibility for protecting the rights and welfare of human research subjects and are responsible for complying with all applicable provisions of their institution’s Assurance.

Investigator Responsibilities Cont.

Investigators are expected to be knowledgeable about the requirements of the Federal regulations, applicable state law, their institution’s Assurance, and institutional policies and procedures for the protection of human subjects.

Investigator’s Responsibilities Cont.

- Conducting their research according to the IRB approved Protocol.
- Ensuring that each potential subject understands the nature of the research.
- Providing a copy of the IRB-approved Informed Consent document to each subject at the time of consent.
Investigator Responsibilities Cont.

- Promptly submitting proposed changes for review prior to implementation.
- Promptly reporting any unanticipated problems and adverse events.
- Submitting the continuing review and study closure forms.

Research Requiring IRB Approval

All research that involves intervention/interaction with human subjects or their identifiable protected health information must be reviewed by the IRB BEFORE it is conducted.

Types of New Studies

- **Exempt** (Virtually No Risk to Humans)
  Short Introductory Questionnaire, Data Collection Sheet...NO INFORMED CONSENT, NO PROTOCOL
  Chair, vice-Chair, or designee reviews

- **Expedited** (Minimal Risk)
  Introductory Questionnaire, Protocol, ICF
  Chair, vice-Chair, or designee reviews

- **Full Board** (Greater than Minimal Risk)
  Introductory Questionnaire, Protocol, ICF
  (Submit approx. 23 days prior to Board Meeting)
  3 Board Members Review
What is Minimal Risk?
(Everyday occurrences)

- Blood draw healthy adults (limits!)
- Observational studies
- Study of data already existing and collected for other reasons.
- Noninvasive "standard clinical tests" MRI
- Non-sensitive questionnaires
- Moderate exercise
- Studies of perception, views, thoughts
- Samples (tooth scrapings, saliva, urine)
- Phase IV post-market study of drugs/devices

Exempt and Non-Human

What is Non-Human Research?

**Non-Human:** The Research team never has contact with subjects OR personally identifiable data (may obtain coded data from another source if a confidentiality agreement is signed, submitted, and approved).
Exempt Criteria

No Subject Identifiers

- Research conducted in established or commonly accepted education setting involving normal educational practices.
- Use of education tests, surveys, procedures, interviews or observation of public behavior.
- Research involving public officials or candidates federal statutes require w/o exception that the confidentiality of the personally identifiable information will be maintained.
- Collection or study of EXISTING data, documents, records, pathological or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the PI in such a manner that subjects CAN NOT be identified, directly or through identifiers linked to the subject.

(Exempt Criteria cont.)

- Research and demonstration projects (Federally funded) which are conducted by or subject to the approval of the department or agency heads, which are designed to study, evaluate or examine: public benefit or service programs; (b) procedures for obtaining benefits or services under these programs; © possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.
- Taste and food quality evaluations.

Exempt in a nutshell:

- Risks to subjects are minimal and the research falls into one of the following categories (these two are most commonly applicable):
  1. Educational, observational, or survey research
  2. Review data that exists at the time of submission to the IRB, AND data is recorded in an ANONYMOUS manner for the research.
Expedited

What is Expedited?

- Research team has contact with subjects OR personally identifiable data but:
  - risks to subjects are no greater than minimal and
  - the research falls into one of the following categories
    1. Collection of blood samples;
    2. Collection of other biological specimens for research purposes through noninvasive means;
    3. Collection of data through non-invasive procedures routinely used in clinical practice;

(Expedited Cont.)

4. Materials (data, records, specimens, and such) collected or will be collected for non-research purposes. Under this category you may collect identifiable information, and you may look at information from any point in time - past, present, or future. You may add new data points to correlate to previously collected data. Because this is more powerful, additional protections are needed. Not only is the paperwork longer, but if you wish to collect information out of the medical record in the future, you will probably need to obtain consent from the subjects!

**Remember - as a clinician you have the right to review your patient's records for treatment, but that right does NOT extend for research purposes. To review medical records for research you must either obtain permission from each individual or a Waiver from the IRB!**
Considerations When Preparing Your Submission

Ethical and Regulatory Considerations

- Would I let a family member take part in the study?
- Is the study design ethical?
- Are the risks worth taking?
- Why is a special population or site included or excluded?

Study Procedures

- In ample detail, establish what really happens, and the risk to subjects.
  - Time commitment.
  - Setting or site.
  - Are "routine" agents used?
  - How is the data analyzed?
  - Logical, chronological, rationalized, and prioritized.
  - Make sure the Consent and Protocol match.
  - Consent form is written at 8th grade reading level.
Qualifications of the Staff

- Confirm the study staff’s duties, qualifications, and roles.

Subject Selection/Enrollment

- How are subjects identified?
  Ads, charts, referrals, own clinic, support groups, public records, etc.
- How many subjects are needed?
  Is there enough to answer the question posed?
- How, when and by whom are subjects first contacted about the study?
  Letter? In person? By whom?

Safety Monitoring

- How is data monitored and by whom?
  • Every study needs a safety monitoring PLAN!
  • Provide objective criteria for withdrawal of subject for safety reasons!
  • Make sure to have stopping rules.
  • Submit necessary reports to IRB!
    (adverse events, deviations/non-compliance, unanticipated problems, revisions, and such)
Risks and Discomforts

- Listed clearly, quantitatively, and in order of seriousness.
- Also consider:
  - The costs and risks of withdrawal of current medications!
  - The non-medical risks (social and psychological).
  - Always guard against potential loss of confidentiality.

Benefits

- Monetary compensation is NOT a benefit.
- State the benefits to individual then to society.

Consent

- Consent is a process not a form but the Form is the formal record/document
- Consent is ongoing
- Timing is important - the details should be submitted
- Anyone who signs a Consent form is considered formally enrolled or whose records are accessed under an approved Waiver
Consenting Cont.

- Adults >18 years of age, sophisticated teens may read adult Form. (Must be written at the 8th grade reading level)

- All minors require parent/guardian to sign

Consider who you have doing the Consenting

- Consent for activities corresponds with their typical clinical practice in medicine.

- Examples:
  - (Breast Study) Mammogram Technologist.
  - (Investigational drugs/devices) Licensed MD

8 Mandatory ICF Elements

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

- Description of Risks;

- Description of Benefits;

- Alternatives to Participation;

- How Privacy and Confidentiality of records will be maintained;
ICF Mandatory Elements Cont.

- An explanation as to whether any compensation and medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

- Who to contact for answers about the research, research subjects' rights, and research-related injury; and

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

6 Additional ICF Elements

- (1) Reproductive risks and risks to an embryo or fetus if the subject becomes pregnant (unforeseeable risks);

- (2) Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent;

- (3) Any additional costs to the subject that may result from participation in the research;

- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation;

- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

- (6) The approximate number of subjects involved in the study.

IRB Submission

https://my.irb.ufl.edu/
What is myIRB?

- Smart Forms, Work Space, Work Flow

VPN outside HSC

- In order to access the system, you need to run the HSC VPN. Download at: [http://vpn.health.ufl.](http://vpn.health.ufl.)
Registration & Login

1. myIRB is located at: https://my.irb.ufl.edu/uflirb/
   a) Vital you get the "s" after http. "S" = secure.

2. The registration link is on the right hand side of the screen.

Inbox / Workspace

Study Smart Forms
Tools: Smart Form Progress

Tools: Print version of Smart Forms
http://irb.ufl.edu/ppt/myIRBprintversion.pdf

Agree to Participate (signature)
Agree to Participate  (study smart form)

Required Training!
- HIPAA for Researchers training
- IRB training
  - HIPAA for Researchers (1 hr) Privacy Requirement – Yearly
  - NIH Extramural Education (2 hrs) or the following CITI modules (Basic IRB Regulations, Informed Consent, History/Ethical Principals) – Every 3 years
  - Local IRB video (1 hr) – Every 3 years

Differences: New Study
- PI proxy
- Investigator designations
  - Old: Co-PI + sub-Investigator
  - New: Co-investigator
- RAC review... in parallel?
Study Workspace

Workflow

Email Notifications

Flexible: set by policy rather than hardwired by programming
Differences: Continuing Review

- Expired:
  - if no CR submitted before expiration – study is irretrievably “closed”.
- New ICF submitted separately as revision

Differences: Revision

- myIRB copies entire study
- Revision may include as many changes to the entire study as you want
- Only 1 revision at a time
  - myIRB can’t reconcile multiple copies
- Can retract, amend, or withdraw revision if needed.

Differences: “Reportable Events”

- Adverse Events, Unanticipated Problems, Noncompliance, and Miscellaneous items
  - Doesn’t copy study, can have as many in process as needed.
Next steps

- Get your team registered

- Insure the PI and study staff have completed their required training
  - Can’t submit without it!

Researcher Manual

- http://irb.ufl.edu/myIRB/manuals/myirbresearchermanual.docx

Finally......

It is not ethical to subject people to risks, discomforts and inconveniences for research that cannot contribute meaningfully to medical science!

It’s up to you to help protect the rights and welfare of human subjects.

If the IRB can’t understand it, the investigator has not done their job.