Research Compliance
when involving Human Subjects

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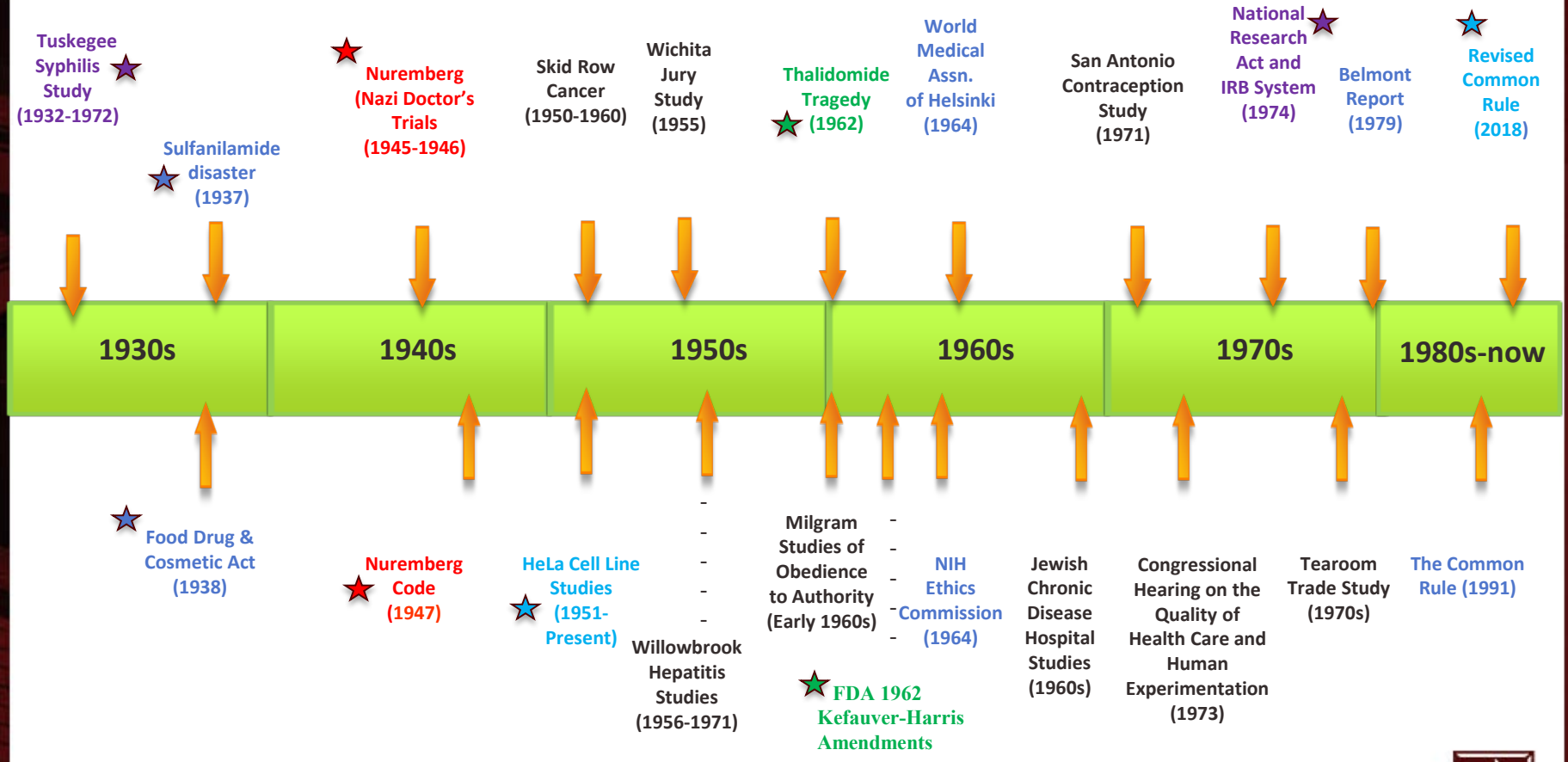
TEXAS A&M UNIVERSITY

Historical Events in Human Research

Advances in protection for human subjects have often come in response to particular abuses or scandals.



Syphilis Study at Tuskegee

- In 1932 the U.S. PHS collaborated with Tuskegee Institute to record the natural history of syphilis.
- 600 black men were enrolled
- The true nature of the study was not disclosed to participants
- This study lasted 40 years and during that time men were misled into thinking they were receiving treatment.
- Penicillin became the drug of choice for treating syphilis in the 1940's but the men were never provided the treatment.
- In the 1960's concerns began to be raised, but the study did not end until 1972.
- In 1973 Congress held hearings.

What Went Wrong?

The men enrolled in the study were:

- never truly informed about the purpose of the study
- never told they could quit the study at any time
- mislead into thinking they were getting treatment
- prevented from getting penicillin from other providers
- allowed to suffer and die with the disease

Resulting legislation:

The 1974 National Research Act - required the use of Institutional Review Boards (IRB) commissioned the Belmont Report and eventually led to the Common Rule.

The Thalidomide Tragedy

- Thalidomide was developed as a tranquilizer in Germany and was sold in Europe and Canada over the counter starting in 1956.
- The drug was soon prescribed off label for pneumonia, colds and flu, and symptoms of nausea during early pregnancy.
- The drug was found to affect normal fetal development
- It is estimated that over 10,000 babies worldwide were affected by the drug.
- The United States was mostly spared from this tragedy because an FDA inspector felt the information on the drug was incomplete and insufficient and would not approve the drug for sale in the United States.

What Went Wrong?

- The effects of the drug had not been fully studied prior to mass distribution
- Lack of proper testing in humans
- The drug was widely accessible

What Went Right?

- Francis Kelsey, MD, PhD of the FDA refused to authorize thalidomide for market because she had concerns about the lack of evidence regarding the drug's safety.

- ***Resulting legislation:*** The 1962 Kefauver-Harris Drug Amendments Act was applied to the 1938 Food Drug & Cosmetic Act. The act required drugs be proven safe and effective through well controlled clinical trials and gave the FDA complete control of drug manufacturing and advertising.

Historical Events in Human Research

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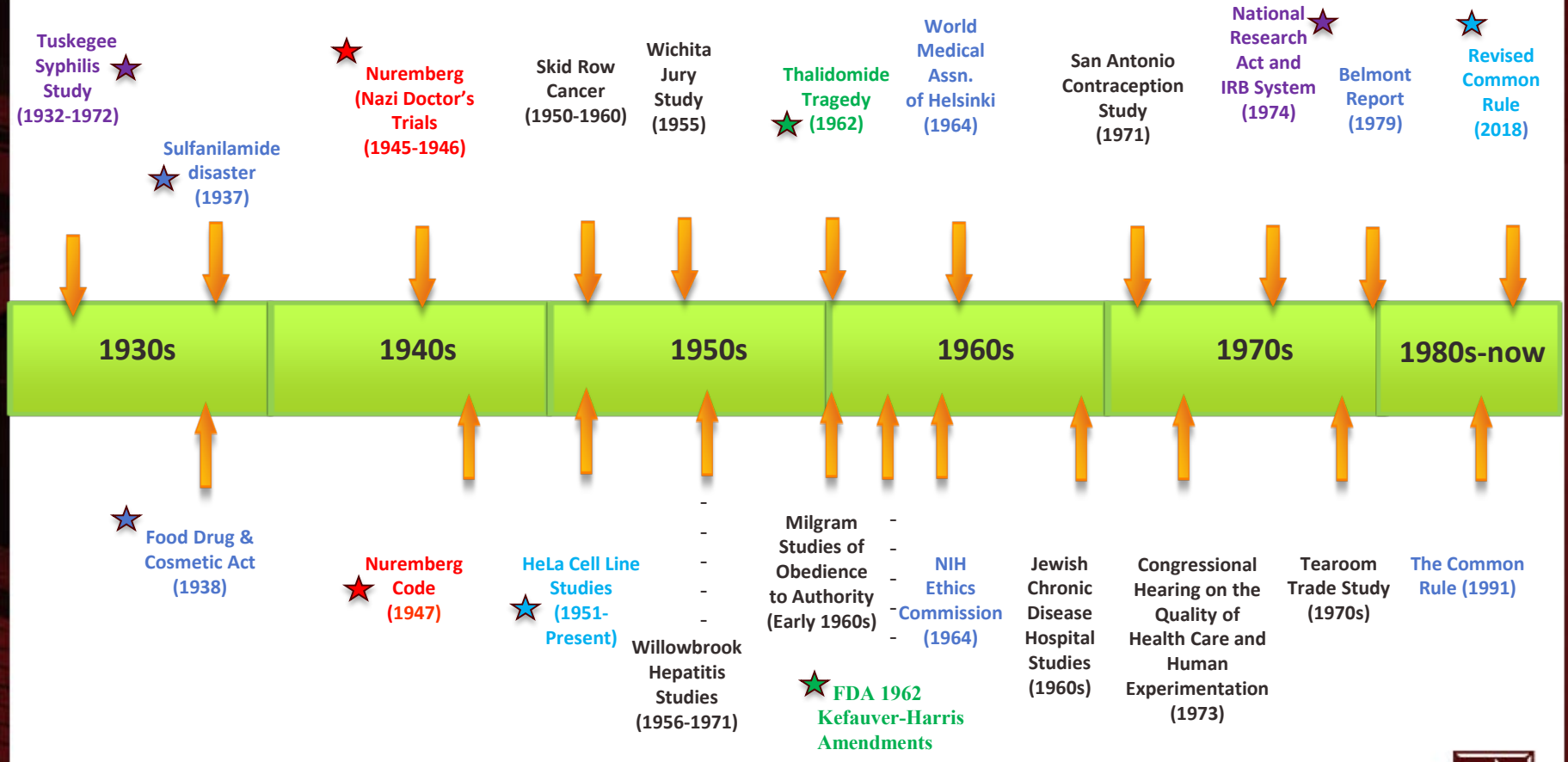
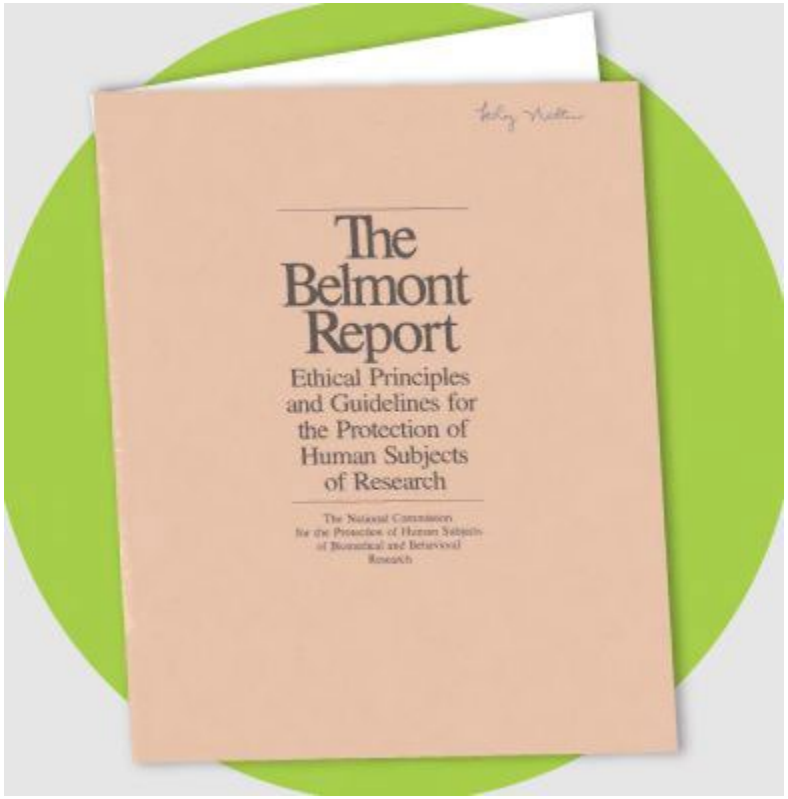


Regulations & Ethical Guidelines
Leading to the Common Rule

- 1974 – National Research Act
- 1979 – The Belmont Report



The Belmont Report's Guiding Ethical Principles

Respect for Persons

- autonomy of subject
- Informed Consent

Beneficence

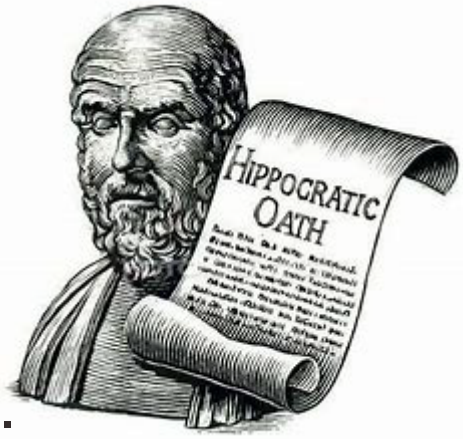
- Maximize benefits, minimize risk of harm

Justice

- selection of subjects is equitable so that benefits and risk are distributed fairly

The ethical principles of the Belmont Report apply to all human research at TAMU regardless of funding even to research that is considered Exempt.

Ethical Guidelines



- The Hippocratic Oath
  was one of first documents
  in history that established
  guidelines related to human treatment.

- The document written around 400 B.C. referred to the same ethical standards used today:
  - do no harm
  - confidentiality
  - justice

Common Rule Timeline

- **1991-** The **Common Rule** - DHHS 45 CFR 46 was formally adopted by more than a dozen of the other federal departments and agencies. Today 17 federal agencies follow the Common Rule.

- **2017 –** The **Revised 2018 Common Rule** was approved and went into effect on January 19, 2019. Revisions addressed ethical concerns related to subject rights regarding personal information or biological specimens. (Changes brought about by high profile cases: Henrietta Lacks; Texas newborn blood spots lawsuit).

- **Note: FDA** has similar rules under Title 21 (food and drugs) **Parts 50 (Protection of Human Subjects)** and **56 (Institutional Review Boards)** that correspond with DHHS regulations.

Highlights of Revised Common Rule

- New categories of activities not human research
- New Definitions (clinical trials, biospecimens)
- Many changes to the exempt categories
- Limited IRB review required for certain exempt categories when information is identifiable
- Continuing review not required for expedited studies
- IRB no longer required to review grants
- Single IRB review for cooperative research (Jan. 2020)
- New requirements for the informed consent document

https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf

Federal Agencies and Departments Adopting the Common Rule (45 CFR 46)

1	Department of Homeland Security
2	Department of Agriculture
3	Department of Energy
4	National Aeronautics and Space Administration
5	Department of Commerce
6	Social Security Administration
7	Agency for International Development
8	Department of Housing and Urban Development
9	Department of Justice (Not the revised Common Rule)
10	Department of Labor
11	Department of Defense
12	Department of Education
13	Department of Veterans Affairs
14	Environmental Protection Agency
15	Department of Health and Human Services
16	National Science Foundation
17	Department of Transportation
18	Office of the Director of National Intelligence
19	Central Intelligence Agency
20	Consumer Product Safety Commission

OHRP

Office for Human Research Protections

A Department of Health and Human Services agency that:

- Requires an institution to obtain and agree to the terms of a *Federal-wide Assurance (FWA*) in order to receive federal funding. *Renewal is every 5 years.*
- Maintains the Common Rule to ensure the protection of human subjects in research.
- Sets forth the requirements for IRB review of human subjects research and requires registration of IRBs
- Requires reporting of certain incidents to OHRP's division of compliance for federally funded studies.

Incidents that Require Reporting to OHRP

- Unanticipated problems that occur in research
- Investigator continuing noncompliance
- Investigator serious noncompliance
- Research suspended by the IRB
- Research terminated by the IRB

Applies to federally funded research. The funding agency must also be notified.

Common Rule
45 CFR Part 46

The Common Rule is divided into subparts: A, B, C & D

Subpart A – Is the core regulation covering the following areas:

- Definitions and Exemptions
- IRB membership
  *(5 members, diversity, scientific, *nonscientific)*
- IRB authority, functions and operations
  (approve, disapprove, require changes, suspend, terminate or observe research)
- Review of Research
  (initial, modifications)
- Criteria for Approval
- IRB Records
- Requirements for Informed Consent and Documentation
- Federal Wide Assurance required for federal funding

I
R
B

Criteria for Approval of Research

The IRB must ensure the following to approve research:

- Risks are minimized; sound procedures
- Risks are reasonable in relation to benefits
- Subject Selection is equitable
- Participation is voluntary and informed consent is obtained, documented or qualifies for a waiver
- Monitor the Data for Safety
- Adequate procedures for Privacy and Confidentiality
- Additional safeguards for Vulnerable Populations

IRB Membership

Each IRB should have at least five voting members:
-Diversity (race, gender, cultural, sensitivity to community attitudes, backgrounds)
    -At least one scientist
    -At least one non-scientist
    -At least one health care professional
-At least one community member who (or his/her immediate family) has no employment or contractual relationships with the entity

-If regularly going to be reviewing vulnerable populations (At least one member who has knowledge and experience on at least one or more vulnerable categories if regularly reviewed

- No IRB may have a member participate in a project review who has a conflict of interest

Authority of the IRB

What authority is given to the IRB by the regulations?

- **Approve research**
- **Require modifications to research**
- **Disapprove research**
- **Suspend or terminate approval of research**
- **Observe the consent process**
- **Observe the research (audit)**

Categories of IRB Review

EXEMPT

- Administrative Determination
- **Minimal risk**
- Educational Research
- Existing data without identifiers
- Simple surveys, interviews

EXPEDITED

- 1 IRB member
- **Minimal risk**
- Annual administrative review
- Non invasive procedures
- Prospective data or retrospective data
- Social Science Methods

FULL BOARD

- Convened Board
- **Greater than Minimal risk**
- No less than annual continuing review
- Clinical Trials
- Sensitive Topics
- Use of Deception
- Non-Compliance

Common Rule - Subparts
45 CFR Part 46

OHRP
Office for Human Research Protections

The Common Rule includes additional protections for vulnerable populations in Subparts B,C and D.

- **Subpart B** - Additional Protections for **Pregnant Women**, **Human Fetuses** and **Neonates** involved in Research
- **Subpart C** – Additional Protections Pertaining to Biomedical and Behavioral Research involving **Prisoners**
- **Subpart D** – Additional Protections for **Children** Involved as Subjects in Research

More Rules and Regulations . . .

- Belmont Report – Autonomy, Beneficence, Justice
- 45 CFR 46 – OHRP Common Rule
- 45 CFR 160 and 164 – HIPAA
- 42 CFR 50 – Conflicts of Interest
- 21 CFR 50 – FDA (Human Protections)
- 21 CFR 56 – FDA (IRBs)
- 34 CFR 99 – FERPA
- 34 CFR 98 – PPRA
- Funding Agency Rules
- Institutional Rules
- HRPP/IRB SOPs

Regulated Products

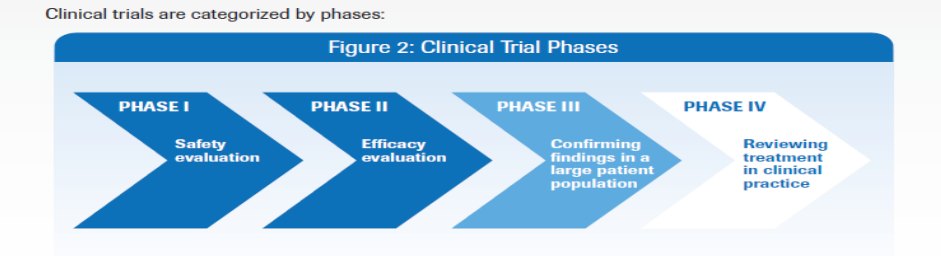
- Drugs, devices, biologics or other treatments (test articles) that are designed to work with the human body.
  - **Drug or biologic** – any article intended for use in the diagnosis, cure, mitigation, cure, treatment of prevention of disease in a human.
  - **Medical Device** – an instrument, apparatus, implement, machine contrivance, implant, reagent, or similar article, part or accessory intended for use in diagnosis, cure, mitigation, treatment or prevention of disease or other conditions in a human.
- **IND - Investigational New Drug Application (21 CFR Part 312)**
- **IDE - Investigational Device Exemptions (21 CFR Part 812)**
- **FDA** regulations add additional criteria for approval that must be satisfied before the trial can begin.

Definition of Clinical Trial

Clinical trial means 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 the interventions on biomedical or behavioral health related outcomes.

Clinical Trial Phases

Regulated by the FDA



Phase	Definition
I	First use with human – usually very small number of healthy subjects; looking at how absorbed, distributed, metabolized
II	First study to focus on clinical effectiveness in patients with the targeted condition; looking at short term side effects, safety risks;
III	Large number of subjects comparing to known effective treatments; application request for license to market
IV	Post marketing studies after approval on thousands of subjects to determine long term safety & efficacy in real world conditions.

Biomedical Research

- **Drugs, Biologics, Dietary Supplements** and any other substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of a disease.
- **Devices** or any other machine, contrivance, implant, in-vitro reagent intended for use in diagnosis of disease or other conditions, or in the cure, mitigation or prevention of disease; does achieve its primary purpose through chemical action; and not dependent upon metabolism for it's purpose.
- **Biological Specimens** – tissue, blood and other bodily fluids.
- Less than 10% of all human research at Texas A&M is biomedical.

Q. When is IRB Review is Required?

A. When an Institution is ‘engaged’ in Human Subjects Research

What is Engagement?

- When Texas A&M University (TAMU) employees or agents are participating in human subjects research activities they are ‘engaging’ the institution in the activity.

- Employees and agents” can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

- Institutions are responsible for the conduct of the research when engaged.

When Are We Engaged?

- **Primary awardees** of funding grants are engaged even when all activities are carried out by employees or agents of another institution/university; or
- **Intervening** with human subjects for research purposes; or
- **Manipulating** a human's environment for research; or
- **Interacting** with humans for research purposes; or
- **Accessing identifiable information** or **specimens** for research purposes; or
- **Obtaining informed consent** or **enrolling** research participants.

Rules of Engagement

- The TAMU IRB/HRPP must be notified when an investigator intends to engage the institution in human subjects research.
- The institution (TAMU HRPP) must document that the research has been reviewed and approved by an IRB or that another type of determination is applicable.
- The institution (TAMU) must verify that all applicable conditions have been satisfied:

  Contracts/agreements, export controls, biosafety, animal welfare, COI, radiation safety, data security, education and training, etc.

We're more than halfway there

- Brief history of the regulations and guidelines for human subject research
- Policies and procedures of the IRB
- Identifying intent: Is this project human subject research?

Q: Which activities require an IRB determination?

A: Activities that meet the ***definition*** of Human Subjects Research

Is it Research?

- The federal regulations define research as:

  “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge" (45CFR46.102(d)).

Does the research involve Human Subjects?

- **Human subject** means a living individual about whom an investigator (whether professional or student) conducting research:

  (1) Obtains *information or biospecimens* through **intervention** or **interaction** with the individual, *and, uses, studies, or analyzes the information or biospecimens*; or

  (2) *Obtains, uses, studies, analyzes, or generates* **identifiable private** information *or* identifiable biospecimens.

Three ways to involve Humans in Research

Intervention	***Interaction***	***Private Information***
using either physical or psychological procedures or manipulations of the subject or the subject's environment.	through communication or interpersonal contact between the investigator and the subject.	observing or recording behavior that is considered private or using private information that is identifiable.

Interventions - *Common Examples*

Testing biomedical or behavioral processes:

drugs
dietary supplements
weight loss strategies
performance strategies
behavioral therapies and testing
cognitive therapies and testing
treatment or prevention strategies

Testing new or revised educational or instructional methods:

students or teachers in classrooms
children or adults in special programs or general public

Human factors evaluation - human experience with:

equipment
systems
technologies

Interaction:

Face to face, phone, remote or online communications for:

- focus groups
- interviews
- surveys

Private Information:

Obtaining identifiable data from:

- medical records
- student records
- research records
- data repositories
- observations/monitoring

Obtaining identifiable human biospecimens (blood or tissue):

- directly from humans, established repositories, secondary use

The IRB application should address the 'Criteria for Approval' with the following as applicable:

- Funding
- Study Personnel and their qualifications (students cannot be Principal Investigators)
- Background & Rationale
- Study Design, Objectives, Hypothesis
- Targeted Study Population
- Recruitment Methods
- Consent Process & Consent Documents
- Procedures (details all procedures that involve humans)
- Risks and Benefits
- Costs to Subjects and any Compensation
- Privacy and Confidentiality
- Data and Safety Monitoring

Submission Documents

Participant Materials

- Recruitment materials
- Consent Documents
- Data Collection Instruments, surveys
- Anything else the participant will see

Administrative Materials

- Grant/Contract
- Thesis/Dissertation Proposal
- Site Authorization or other approvals
- Drug/Device Labels and brochures

Investigator Obligations

- *Follow the approved protocol*
- *Amendments*: Submit any changes to the IRB for review and approval prior to implementation.
- Submit a *Continuing Review or Administrative Check-in no less than annually*
- *Report* any unanticipated problems, deviations, complaints and other reportable items.
- Keep Records of all study activity including:
  - IRB correspondence
  - consent and study documents
  - Keep track of participation numbers, reasons for withdrawals, complaints, unanticipated problems. Be audit ready at all times.
- Close – out by submitting a *completion report* when all study procedures including data analysis are done.

Investigator Obligations
Required Training

- Ethics Training required before submission
  - Web-based ethics course www.citiprogram.org
    - Group 1: Biomedical Research Investigators and Key Personnel
    - Group 2: Social and Behavioral Research Investigators and Key Personnel
  - Must be renewed every five years
  - Conflict of Interest Training
  - HIPAA Training
  - More information available at: http://rcb.tamu.edu/humansubjects/training

Human Research Protection Program

General Contact Information

Phone: (979) 458-4067

Fax: (979) 862-3167

Email: irb@tamu.edu

Location: Blocker Building

155 Ireland Street

Room 228