HUMAN SUBJECTS RESEARCH AT MICHIGAN STATE UNIVERSITY

Becky Gore
Judy McMillan
HAVE YOU SUBMITTED AN APPLICATION TO THE IRB BEFORE?

1. Yes
2. No
Have you participated in a research study before?

1. Yes
2. No
Today’s Topics

- Group Discussion Scenario
- History of Human Subjects Protection in the United States
- Federal Regulations and Guidelines
- MSU Policies
GROUP DISCUSSION SCENARIO
PLEASE SELECT A TOPIC...

1. Domestic Violence
2. Illegal Drug Use
3. Heart Disease
4. Mental Illness
PLEASE SELECT A SETTING...

1. Hospital
2. Prison
3. K-12 School
4. Corporate Office
Please select a location...

1. Michigan
2. Texas
3. China
4. Malawi
PLEASE SELECT AN AGE GROUP

1. 0-5
2. 12-18
3. 18-24
4. 65-99
PLEASE SELECT AN ACTIVITY

1. Interview/Survey
2. Videotaping
3. Review of Medical Records
4. Drug Study
Please Select ...

1. Will I
2. Or won’t I ...
PLEASE SELECT …

1. Will it
2. Or won’t it
SCENARIO

Dr. Smith will be conducting research on ________ (select a topic).

The subject population will be ____________ (select an age range).

The research will involve _________ (select a type of research intervention). Subject names __________ (select will / won’t) be recorded.

The research will be conducted at _________ (select a location) located _________ (select a location).

There ____________ (is / is not) potential for direct benefit to the subject.

What are potential issues with . . .

- Risks and benefits
- Privacy and Confidentiality
- Informed consent
- Selection of subjects
- Others?
History of Human Subjects Protection in the United States
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research established by Congress in 1974 as a response to:

- Tuskegee syphilis study
- Psychosurgery
- Research with prisoners
- Research with people with mental impairment
- Fetal research – research on the human fetus after abortion (just after Roe vs Wade in 1973)
WHAT IS ETHICAL RESEARCH?

- Major ethical principles in research
  - Respect for Persons
  - Beneficence
  - Justice

- The commission named the above, as the major principles, but not the only ones ...
  - Truth – honesty
  - Fairness
  - Integrity, etc.

- Largely responsible for starting the field of bioethics in this country
Tangible results of Belmont and the Federal regulations

Human Subjects Research

Evil and Scary 1970s

Contrast public opinion regarding Tuskegee to AIDS research today....

Good and reputable 2015
Tuskegee Syphilis Study

- Funded by the U.S. Public Health Service

- Studied progression of syphilis in African American men

- Study design:
  399 subjects with syphilis
  200 controls

- Deception:
  - Subjects thought that they were receiving beneficial medical care, even given a lumbar puncture to see the advancement of the disease – they were told it was for treatment
  - Followed, untreated, for years after penicillin was known to cure syphilis
**IMPORTANT DATES**

- January 1930 – one year syphilis demonstration project in Macon County (where the researchers treated the disease)
- October 1932 – study begins
- 1936 – first journal article gets published – medical community very aware of the study
- **1943 PHS (public health service) starts using penicillin**
- WWII draft – arrangements made not to draft men in syphilis study
- 1947 Nuremberg Code
- 1958 PHS distributes certificates of appreciation and $25 dollars to participants
- 1964 The World Health Organization issues the Declaration of Helsinki
- February 1969 CDC Committee, with one dissent, votes to continue study
- July 25, 1972 – AP story breaks Washington Star
- **March 1973 HEW authorizes treatment**
- December 1974 10 million dollar law suit is settled – no criminal or civil liability for researchers
- May 16, 1997 – President Clinton apologizes
I HAVE A DREAM ....

Martin Luther King's Address at March on Washington

Meanwhile the men in Tuskegee would still not receive treatment for another 10 years ....
Guatemalan study – President Obama has responded with the Presidential Commission for the study of Bioethical Issues

Principal Investigator: Dr. Cutler and Venereal Disease Research Laboratory

Studies involved: syphilis, gonorrhea and other STDs

Subjects: prostitutes, prisoners and people with mental health disorders

Nobody was consented, and people were inoculated with STDs
MILGRAM STUDIES (1960s)

- **Purpose:** Understand why people follow the directions of authority figures even when they are told to do things that are cruel or unethical.
- **Method:** Subjects were instructed to deliver, at increasingly higher intensities, shocks to others.
- After they were “debriefed,” subjects complained of extreme psychological distress after understanding the potentially lethal level of shocks administered.
SAN ANTONIO CONTRACEPTIVE STUDY (1970s)

- Purpose: Determine efficacy of different kinds of contraceptive pills
- Population: Predominantly indigent patients who had no other place to go for contraceptive advice/medication
- Method: Randomized design. Some subjects received placebo.
- Result: High number of unplanned pregnancies in placebo group.
THE FEDERAL REGULATIONS
U.S. Federal Regulations for Human Research

- Health & Human Services, 45 CFR 46
  - [http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)

- Food & Drug Administration, 21 CFR 50, 56

- Other U.S. regulatory agencies have human subject protection regulations (e.g., Dept. of Education, Dept. of Justice, etc.) but most have adopted some or all of 45 CFR 46 (known as the Common Rule)
Subpart A – The Common Rule
basic set of protections for all human subjects of research conducted or supported by HHS (1974, revised 1981, 1991, 2005)

Subpart B – pregnant women, human fetuses and neonates (1975, revised 2001)

Subpart C – prisoners (1978)

Subpart D – children (1983)

Subpart E – requires registration of IRBs (2009)
WHAT IS RESEARCH?

*Research* means a *systematic investigation*, including research development, testing and evaluation, designed to develop or contribute to *generalizable knowledge*. [45 CFR 46.102(d)]

**IMPORTANT:**

1. At MSU, “research" includes the preparation of Masters Theses & Doctoral Dissertations.
2. FDA “clinical investigations” involving “human subjects” also require IRB review
YOU HAVE A CHANCE TO INTERVIEW TWO PIRATES AND WANT TO WRITE AN ARTICLE FOR THE LOCAL NEWSPAPER.

Is the activity research?

1. Yes
2. No
For his Ph.D. dissertation, Sam Student is going to be studying factors that affect high school achievement and performance. Methods include surveying students, examining grades and other high school records, and giving a standard psychological exam.

Is the activity research?

1. Yes
2. No
DOES THE RESEARCH INVOLVE A HUMAN SUBJECT?

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

(1) Data through *intervention or interaction* with the individual, or
(2) *Identifiable private information*.

[45 CFR 46.102(f)]
A researcher wants to obtain samples from deceased individuals with pancreatic cancer for analysis related to their disease.

Is the activity research with human subjects?

1. Yes
2. No
Now Remember:

Research + Human Subjects = IRB Review
OHRP WEBSITE

- Regulations
- Policy & Guidance to help interpret how to apply the regulations
- Frequently asked questions
- Several educational videos
- Flow charts – to help determine if your proposal has to be reviewed by the IRB

http://www.hhs.gov/ohrp/
Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration...

The activity is FDA regulated if either of the following are true for drugs:

- The drug is not approved by the FDA for marketing.
- The drug is not being used in the course of medical practices.
IS THE ACTIVITY A CLINICAL INVESTIGATION?

A physician at MSU has tried every standard therapy to treat her patient but nothing already on the market is working. The physician has heard colleagues at professional meetings talk about good results from a new drug approved to treat a different disease. Desperate to help her patient, the physician prescribes the drug, even though the outcome is uncertain.

Clinical Investigation?
1. Yes
2. No
CLINICAL INVESTIGATIONS OF DEVICES REGULATED BY THE FDA

The activity is FDA regulated if either of the following are true for devices:

1. Clinical investigations of devices to determine safety and effectiveness.
2. Tissue specimens are being held to test the effectiveness of a medical device (including in vitro diagnostic devices) and the information is being submitted to the FDA for FDA approval of the device.
SO YOU DETERMINED YOU ARE DOING RESEARCH AND IT INVOLVES HUMAN SUBJECTS

- Now what?

Submit application online.
What does the IRB do .......
IRB REVIEW OF RESEARCH

- An IRB shall review and have authority to approve, require modifications (to secure approval), or disapprove all research activities covered by this policy.
- Either require informed consent or waive it.
- An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity.
- Provide continuing review at intervals appropriate to the risk but not less than once a year.

[45 CFR 46.109]
What is the IRB?  
Institutional Review Board

- At least five members
- Varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution
- Qualified by experience and expertise Diversity of members including considerations of race, gender and cultural backgrounds
- At least one member whose primary concerns are in scientific areas and one whose primary concerns are nonscientific
- At least one community member (who is not affiliated with the institution or immediate family is not affiliated)
- Prisoner representative if prisoner protocols are discussed

[45 CFR 46.107]
46.111 Criteria for IRB approval of research

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent will be sought and documented from each subject or the subject’s legally authorized representative
- The IRB must decide if a data monitoring plan is needed
- When appropriate, there are provisions to protect the privacy of subjects and to maintain the confidentiality of the data
- Vulnerable populations are protected

[45 CFR 46.111]
46.116 – Informed Consent

- 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;
- Reasonably foreseeable risks and benefits;
- Disclosure of appropriate alternative procedures, if any;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- If research greater than minimal risk – an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- An explanation of whom to contact about research and research subject’s rights, and whom to contact in the event of a 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.
ADDITIONAL ELEMENTS AS REQUIRED BY IRB
[45 CFR 46.116]

- Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

  (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

  (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 by the subject;

  (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.
WAIVER OF CONSENT – SUBPART A

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

- Minimal risk
- Not adversely affect rights & welfare of subject
- Research could not practicably be carried out without the waiver
- Provide additional information as appropriate

[45 CFR 117(c)]

FDA – exceptions to informed consent
MSU IRBs

- MSU Institutional Review Boards
  - Biomedical and Health Institutional Review Board (BIRB)
  - Social / Behavioral / Education Institutional Review Board (SIRB)
  - Community Research Institutional Review Board (CRIRB)
- Chairs of the IRBs:
  - SIRB – Harry McGee, MPH
  - BIRB/CRIRB - Ashir Kumar, MD
**MSU Policies and Procedures**

- Each institution that has an IRB must have their own policies and procedures [46.108]

- MSU HRPP Manual

- Specific MSU Policies
  
  - MSU IRB Chair/Staff determines whether a project is human subjects research
  
  - If it is human subjects research, the MSU IRB Chair/Reviewer/Staff can determine the appropriate level of review
    - Exempt
    - Expedited
    - Full Review
TRAINING REQUIREMENTS

- All individuals who have contact with human subjects or their identifiable data must have current IRB training
  
  - Initial training: Completion of the MSU IRB online tutorial. Valid 2 years.

  - To renew training: Complete 6 CITI program modules prior to training expiration date.

TRAINING REQUIREMENTS

- The Michigan State University Human Research Protection Program (HRPP) is in the process of expanding training and education options through the Office of Regulatory Affairs (ORA) Saba training system.

- The first phase of implementation will transition IRB training records and modules to the Saba training system. Implementation is expected in July 2015.

- In the second implementation phase, optional modules on specialized topics will be made available. If you have topic suggestions for optional modules, please email us at hrpp@ora.msu.edu.
Differences in Review Levels

- Non Human Subjects Research – No further contact with the IRB

- Exempt [45 CFR 45.101(b)]
  - PI Assurance
  - Consent process – less required elements
  - Revisions: check with IRB when you make changes to protocol – in case change should change review category or degree of risk (email)
  - Renewals: no renewal needed – IRB does not actually approve the project but determines it exempt
  - Closure: None
EXPEDITED OR FULL REVIEW – FEDERAL REQUIREMENTS APPLY

• Expedited [45 CFR 46.110] – Minimal risk
  • Review process -- by chair and/or an IRB committee member
  • Consent process -- requires all the federally mandated elements plus additional MSU elements (dateline, written in the second person, age appropriate assent, conflict of interest, written in lay language, audio/video recording procedures, do not use- ‘understand’, IRB endorsement)

• Full Review [46.108(b)] – Above minimal risk or research with vulnerable populations
  • Review process – Full board reviews will be assigned to a subcommittee of 3 IRB members; initial approval and renewal but must be approved by the Full Board
  • Consent process – same elements as expedited
Minimal Risk?

“Minimal risk means that the probability & 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.” [45 CFR 46.102(i)]
Continuing Responsibilities

- **Revisions (through online system)**
  - obtain approval for changes before implementing them

- **Renewals (through online system)**
  - obtain renewal for your study before approval expires

- **Unanticipated Problems and Adverse Events (download form)**
  - report unanticipated problems that may involve risks to subjects or others immediately to the IRB
  - completed forms can be submitted via the Responsible Investigator’s MSU email account

- **Closures (download form)**
  - communicate the completion of your study to the IRB
  - completed forms can be submitted via the Responsible Investigator’s MSU email account
OTHER RESPONSIBILITIES

- Protocol Deviations/Violations
- Subject Complaints (HRPP manual 9-4)
  - Reported to the IRB or investigators
    - IRB chair evaluates the complaint
      - Risk?
      - Protocol deviation?
      - Change to protocol needed?
      - Immediate action needed?
      - Consult IRB?
- Audits
  - Regulatory requirement – 45 CFR 46.109(e)
- Non-Compliance
  - Serious
  - Continuing
INTERNATIONAL RESEARCH

- Research conducted outside of the United States must conform to the same ethical standards, university policies and regulatory standards to which research conducted within the US is held.

In addition:
- Local Ethics Boards
- Consulting an Expert
CLOSING A PROTOCOL

- **Anonymous (De-Identified) Data**
  - Close the protocol as soon as you are finished interacting with subjects

- **Identifiable Data**
  - Close the protocol when you can no longer link a subject’s identity to a particular dataset (for example, large number of subjects with a code if the key has been destroyed)

- **Permanently Identifiable Data**
  - Close the protocol when you are finished analyzing the data (qualitative studies, with a small number of subjects)
RECORD KEEPING

- IRB
  - Maintain File –
    - Electronic for Exempt protocols
    - Paper for Expedited and Full review
  - IRB Minutes

- Principal Investigator
  - Confidentiality of Records
  - Retain records for at least three years after closing protocol
MSU Resources

- IRB Main Office: 207 Olds Hall
  - Located between the Administration bldg. and the main Library
- IRB phone number: 517-355-2180

- IRB Website: http://www.hrpp.msu.edu
  - Consent templates: http://hrpp.msu.edu/forms

- OHRP Website: http://hhs.gov/ohrp