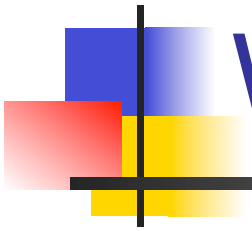

# Working with Human Subjects

CSCI 4800/6800

Spring 2007

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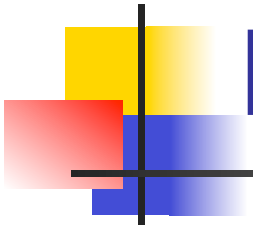
# Research Oversight

- Research involving human subjects require oversight
  - Why?

# Why is oversight needed?

- Human subjects have not always been well protected.
- Privacy issues for individuals are a growing social concern
- Research is big business with substantial financial interests.
- The future impact of such issues as genetic engineering, cloning, gene therapy, pharmacogenomics, etc. is unknown.



# History

- Celsus, 1st century physician
  - perfomed experiments on condemned criminals in Egypt
- His defense:
  - "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries."
- Times have changed ….

# History – Nuremberg Code

- At the end of World War II, 23 Nazi doctors and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects.
  - However, no accepted standards existed regarding the conduct of human research.
  - The court found that it could not convict the defendants of violating the rights of research subjects.
  - However, the court did convict 15 of the 23 defendants of murder. Result:
    - 7 condemned to death by hanging
    - 8 sentenced to prison from 10 years to life
    - 8 acquitted

# History – Nuremburg Code

- The court included in its judgment ten points describing required elements for conducting research with humans. These points became known as the Nuremberg Code, and included the following ideas:
  - Informed consent is essential.
  - Research should be based on prior animal work.
  - The risks should be justified by the anticipated benefits.
  - Only qualified scientists must conduct research.
  - Physical and mental suffering must be avoided.
  - Research in which death or disabling injury is expected should not be conducted.

# Effect of the Nuremberg code

- The Code had little impact on researchers in the United States, who thought that:
  - the principles in the Code were already implicit in their work
  - it was simply a document to condemn the Nazi atrocities and to convict the Nazi doctors.
- Problems with the code:
  - did not have the strength of law
  - applied to only non-therapeutic human subjects research.

# History: Declaration of Helsinki

- 1964 - the World Medical Association develops a code of research ethics which came to be known as the Declaration of Helsinki.
- reinterpretation of the Nuremberg Code + addressed medical research with therapeutic intent.
- Journal editors began to require that research be performed in accordance with the Declaration.

# History: Beecher Article

- Beecher HK. " Ethics and Clinical Research" NEJM June 16, 1966
  - described 22 examples of research studies with controversial ethics that had been conducted by reputable researchers and published in major journals.
  - "medicine is sound, and most progress is soundly attained;" However, if unethical research is not prohibited it will "do great harm to medicine.“
  - heightened awareness to the problem of unethical human subjects research

# The Public Health Service Syphilis Study (1932-1971)

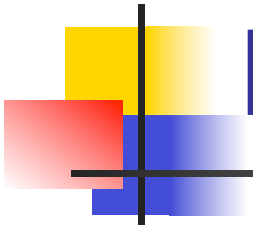
- a.ka. - "Tuskeegee Syphilis Study"
- designed initially to make treatment available to African-American men with syphilis, although at the time the study began there was no known effective treatment.
- After funding to make drugs available was cut, the study became a natural history study. Hundreds of men with syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study.

# Tuskegee Syphilis study

- men were recruited without their informed consent
- were deliberately misinformed about the need for some of the procedures.
  - e.g., spinal taps were described as necessary and special "free treatment."
- Even after penicillin was found to be a safe and effective treatment for syphilis in the 1940's, the men were denied antibiotics.
  - Collusion with military and local doctors to prevent treatment.
  - Continued until 1972.
  - Resulted in 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis (children born with syphilis)

# Tuskegee Syphilis study

- *Ethical problems*:
  - lack of informed consent
  - deception
  - withholding information
  - withholding available treatment
  - putting men and their families at risk
  - exploitation of a vulnerable group of subjects who would not benefit from participation.



# But …

- that sort of thing couldn't happen now, could it??

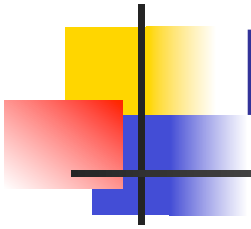
# Recent Events: Death of a Normal Volunteer

- March 1996, 19-year-old student at University of Rochester responds to advertisement for subjects to undergo bronchoscopy for the harvest of alveolar macrophages.
- bronchoscopy was difficult and required numerous doses of topical lidocaine.
- The investigators repeatedly asked the subject if she wanted to continue and the subject nodded her head "yes."
- subject later suffers from overdose of lidocaine
- dies 3 days later
- Problems:
  - protocol did not limit lidocaine doses
  - doses were not documented
  - subject was not observed after the bronchoscopy
  - concentrations of lidocaine were increased without IRB approval.

# Recent Events: Death on Gene Therapy Trial

- 1999, eighteen-year-old dies as a result of participation in a gene transfer trial.
- participant had a rare metabolic disorder, ornithine transcarbamylase deficiency syndrome (OTC) that was being controlled by medication and diet. Researchers were testing an innovative technique using adenovirus gene transfer.
- participant experienced multiple organ failure and subsequently died.

- Serious concerns:
  - conflict of interest
  - data safety monitoring
  - informed consent



# But …

- We’re not doing medical research, why should we be concerned??? …

# Wichita Jury Case (1953)

- researchers tape recorded jurors' deliberations in six courtroom trials to measure the influence of attorney comments on decision making.
  - judge and attorneys knew the research was being conducted, but the jurors did not.
  - The tapes were played at a law conference.
  - Concern: future taping could have a repressive effect on juror deliberations
  - Result: federal law banning all recording of jury proceedings
  - *Ethical problems*: compromising the integrity of important social institutions, lack of informed consent, invasion of privacy.

# Milgram “Obedience to Authority Study” (1963)

- Purpose of study - to learn more about how humans respond to instructions from people in positions of authority.
- volunteers told that purpose of the research was to study learning and memory.
- Each subject was told to teach a "student" and to punish the students' errors by administering increasing levels of electric shock.
- The "students" were working with the researcher
  - were never actually harmed
  - pretended to be poor learners
  - mimicked pain and even unconsciousness as the subjects increased the levels of electric shock.

# Milgram study, continued

- Sixty-three percent of the subjects administered what they thought were lethal shocks; some even after the "student" claimed to have heart disease
- Some of the subjects, after being "debriefed" from the study experienced serious emotional crises.
- *Ethical Problems:* deception, unanticipated psychological harms.

# Zimbardo "Simulated Prison" (1973)

- landmark psychological study of the human response to captivity and, in particular, prison life, involved assigning roles to male student volunteers as "prisoners" and "guards".
- The research became so intense, as physical and psychological abuse of "prisoners" by "guards" escalated, that several of the subjects experienced distress less than 36 hours after the study began.
- Dr. Philip Zimbardo, the researcher, failed to stop the experiment/simulation until six days had passed.
- *Ethical problems*: harm to subjects, neutrality of researcher.

# Restaurant Letter Study (2001)

- faculty member from a university Business School conducts study to elicit responses from restaurants to complaints from customers.
- sent letters to restaurants falsely claiming that he and/or his wife had suffered food poisoning that ruined their anniversary celebration.
- disclaimed any intention of contacting regulatory agencies and stated that the only intent was to convey to the owner what had occurred "in anticipation that you will respond accordingly."

# Restaurant letter, cont'd

- Restaurant owners and employees suffered severe emotional distress before learning that it was a hoax.
- The researcher later admitted the falsehood in a letter of apology. He explained that "the letter was fabricated to help collect data for a research study that I designed concerning vendor response to customer complaints."
- Study had not been submitted to an IRB for review. An investigation by the Federal Office for Human Research Protections (OHRP) followed.
- The restaurants filed a lawsuit against the University.
- *Ethical problems*: Deception, lack of informed consent, infliction of emotional distress.

# As a result of events of this type…

- National Research Act of 1974
  - Established “National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research”
  - Required establishment of IRBs at institutions receiving US Department of Health, Education and Welfare (now the Department of Health and Human Services) funding for human subjects research

# The National Commission asked to..

- Identify the basic ethical principles that underlie the conduct of human research
- Develop guidelines to ensure that human research is conducted in accordance with those principles

- This work led to the current federal regulations.

# Consequences

- The government issued a report in 1979, known as the Belmont Report
- The Belmont Report established the basis for the ethical principles upon which federal regulations for protection of human subjects are based.
- Anyone who does human subjects research should read it!

# The Belmont Report

- http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

# Principles of the Belmont Report

- Respect for Persons
- Beneficence
- Justice

- In practice, need to balance these three principles

# Respect for Persons

- Researchers must treat individuals as autonomous human beings, capable of making their own decision/choices, and not use people as a means to an end.
- Extra protection for those with limited autonomy.

# Elements of autonomy:

- Mental capacity (the ability to understand and process information)
- Voluntariness (freedom from the control or influence of others)
- Subjects have full autonomy when they have the capacity to understand and process information, and the freedom to volunteer for or withdraw from research without coercion or undue influence from others.

# Rules derived from principle of respect for persons:

- The requirement to obtain and document informed consent.
- The requirement to respect the privacy interests of research subjects.
- The requirement to consider additional protections when conducting research on individuals with limited autonomy.

# Beneficence

- Researchers should minimize the risks of harm and maximize the potential benefits of their work.
- researchers and IRBs should conduct a careful assessment of the risks of harm and the potential benefits of the research
- potential benefits should justify the risks of harm.

# Beneficence, continued

- "risk" refers to possibility that harm may occur
- requires evaluating both magnitude and likelihood of harm
  - harms include not only physical, psychological, legal, social, and economic harms.
- "benefit" refers to something of positive value related to health or welfare.
  - Can accrue to individual subjects or to others, such as a community, or humanity as a whole.
- In general, the risks and benefits to the individual subjects carry more weight than benefits to others.

# Rules derived from principle of beneficence

- The requirement to use procedures that present the least risk to subjects consistent with answering the scientific question
- The requirement to gather data from procedures or activities that are already being performed for non-research reasons.
- The requirement that risks to subjects be reasonable in relation to both the potential benefits to the subjects and the importance of the knowledge expected to result.

# Rules derived from principle of beneficence

- The requirement to maintain promises of confidentiality.
- For research that involves more than minimal risk of harm, the requirement to monitor the data to ensure the safety of subjects.

# Justice

- Researchers must treat people fairly and design research so that its burdens and benefits are shared equitably.
- Those who benefit from the research should share in the burden of being subjects in the research.
- Those who serve as subjects in the research should share in the potential benefits from the research.

# Justice, continued

- Individuals or groups should not be selected for research participation solely because they are available, cannot say no or do not know that they can say no.
- In order to avoid exploitation the selection of subjects should solely based on scientific justification.

# Rules derived from principle of Justice

- The rules derived from justice include:· The requirement to select subjects equitably.·The requirement to avoid exploitation of vulnerable populations or populations of convenience.

# The Common Rule

- Protective mechanisms established by the Common Rule (45 CFR 46):
  - Review of all research by an IRB
  - Informed consent must be obtained from subjects prior to research
  - Institutional assurances of compliance

# Some basic definitions:

- **Research**

  Research is a systematic investigation designed to discover or contribute to a body of generalizeable knowledge.

  When research involves human participants, the researchers and their team are legally and ethically obligated to protect the participants.

# Research participant

- A research **participant** is a living individual about whom a researcher obtains either:

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

# When does research require protection of human subjects?

- **Any** study intended to result in publication or public presentation, including classroom projects.
- **Any** activity resulting in publication or public presentation, even though it involves only review of existing data that was collected with no intent to publish.
- **Any** use of an investigational drug or device.

# Studies not considered research

- If an activity is not research, it does not require IRB approval.
  - Examples would be employee evaluation, program evaluation, quality assurance, or other situations where such evaluation is not designed to lead to generalizable knowledge.

# Vulnerable populations

- By Federal definition, some populations require special protection:
  - Children
  - Persons with diminished capacity to consent
  - Prisoners
  - Fetuses and pregnant women
  - Terminally ill persons
  - Students or employees
  - Comatose patients

# The Institutional Review Board

- Mandated for all institutions conducting human research.
- Composition of Board, functions of board, reporting requirements for board are all mandated by Office of Human Research Protection (OHRP).

# Role and Responsibility of IRB

- Review research plan to be sure it meets criteria in Federal regulations (45CFR 46.111)
- Confirm there are no unreasonable risks
- Conduct continuing review
- Assess suspected or alleged protocol violations.

# IRB Composition

- According to Common Rule, the IRB must
  - Be representative of community
  - Must have at least five members
  - Include one scientist
  - Include one nonscientist
  - Include more than one profession
  - Include one person not affiliated with the institution.

# Authority of IRB

- The IRB has authority to:
  - Approve, disapprove, or terminate all research.
  - Require modifications to protocols.
  - Require that information the IRB deems necessary is provided to participants.
  - Require documentation of informed consent, or allow waiver of consent.

# Submitting protocols for review

- All listed researchers must complete ethics training prior to submission.
- Protocols submitted to Human Subjects Office for approval.
- All listed researchers must complete ethics training prior to submission.
- Student projects must be approved by research supervisor or advisor.

# Types of IRB Review

- Full board review
- Expedited review
- Administrative review

# Full board review (quorum review)

- Quorum review is review of a protocol by a quorum of IRB members attending the monthly IRB meeting.
- Necessary for research involving risk of physical or psychological harm greater than that encountered in daily life, particularly research involving deception, stress, or manipulation.

# Expedited review

- All research activities must be no more than minimal risk and belong in one or more of the following categories:
  - Collection of data through noninvasive procedures, such as weight, blood pressure, muscle strength testing, flexibility testing, etc)
  - Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes.

# Expedited review (cont'd)

- Voice, video, digital, or image records made for research purposes.
- Group or individual characteristics or behaviors
- Continuing review of research previously approved by quorum review in some instances.

# Expedited Review

- Does not require review at full board meeting
- Does require review and approval by one or two board members.

# Administrative review

- Exempt research does not require expedited or quorum review by the IRB, but it does require “exemption approval” at the institution level.
  - Research involving the collection or study of existing data, including documents, records, not collected in a prospective fashion (e.g. the data must exist before the research is initiated);

# Administrative review

- Criteria (continued)
  - Research conducted in accepted educational settings
  - Research involving only the use of educational (diagnostic, aptitude, or achievement) tests.
  - Research involving only observation of public behavior
  - Research involving only surveys or interviews (for participants over age 18)
  - Research involving only taste and food quality evaluations.

# Administrative review

- Any research in which the subjects or their legal representatives sign a consent form cannot qualify as exempt and must undergo expedited or quorum review.
- Studies involving the audio/videotaping or surveys/interviews of students under age 18 are never exempt.

# Protocol Preparation

- All protocols must contain the following elements:
  - Protocol statement (What is to be done.)
  - Abstract
  - Consent and assent forms
  - Discussion
  - Attachments

# Protocol Statement

- First two pages of protocol
- Title
- Investigators
- Review category requested
- Estimated Starting date
- Reasons for conducting research
  - Professional
  - Dissertation Research
  - Class assignment (provide name of faculty)

# Protocol statement

- All personnel involved
- Location for study
- Special populations, if any
- Items of special concern
  - Questionnaires
  - Filming, videotaping,
  - Deception of subjects
  - Use of placebos
  - Several other items.

# Protocol Statement

- Method of obtaining consent
- Method of obtaining assent
- Recruitment ad – all ads need IRB approval.
- Source of funding
- Financial issues
- Signatures

# Abstract

- A brief summary of the proposal, written in lay language, of the purpose and procedures to be followed.
- It should be no more than 250 words.
- If not in lay language, staff may return without IRB action.

# Consent and assent forms

- See next section for extended discussion

# Discussion (Elements)

- Purpose and procedures
  - State the specific aims of the project. Provide the scientific basis for conducting study if appropriate (literature references may be useful). Describe procedures and indicate location of study.
- Subject
  - State the proposed number of subjects, criteria and methods for recruiting, selecting, and excluding subjects.

# Discussion

- Payment to subjects
- Costs to subjects
- Benefits to subjects
- Risks and discomforts
- Alternatives
- Radiation (if present)
- Infective agents or biohazards

# Discussion

- Future additional information – how it will be disseminated to subjects
- Deception (if deception is employed, need quorum review)
- Debriefing (if deception is involved)
- Intervention – describe any interventions that must be legally required or ethically appropriate.

# Discussion

- Confidentiality – Explain how confidentiality will be maintained for records, videotapes, audiotapes, and how records will be destroyed at end of study.
- Qualifications of Principal Investigator
- Qualifications of other investigators.
- Role of any other participants listed in protocol.

# Attachments

- Provide any advertisements or telephone or radio texts to be used in recruitment.
- Provide letter from a school or other institution where study is to be conducted giving approval to use facilities using the facilities letterhead.
- Provide a copy of each survey or other forms.
- Provide any other appropriate documents.

# Informed Consent

- After defining research questions and establishing a valid design and protocol, next step is to plan how to obtain informed consent for those invited to participate.

# Informed Consent

- A process instead of a form.  The form is documentation of the process.
- Plan must be reviewed and approved by the IRB before approaching potential subjects.
- There are a number of required elements and standard language that must be used.
- Check Compliance Office website or contact persons in compliance office.

# Consent Form

- Information to be included:
  - Statement that study is research
  - Definition of the study
  - Invitation to participate and why individual has been selected.
  - Anticipated duration of study
  - Description of procedures, including explanation of placebo or randomization, if appropriate.

# Consent form

- Description of foreseeable risks or discomfort and what steps will be taken to minimize these risks
- Description of benefits, if any
- Discussion of appropriate alternate procedures – Not to participate is always an alternate.
- Statement regarding confidentiality.

# Consent Form

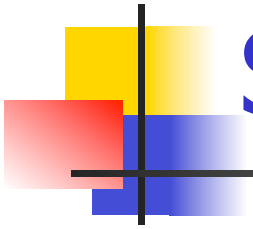
- If more than minimal risk, explanation of compensation and medical treatment to be expected.
- Statement that participation is voluntary
- Statement that refusal to participate or withdrawal from study will involve no penalties or loss of benefits, placement, class standing, grades, etc.
- Must be written in lay language at approximately Grade 8 level.

# Consent Form

- Statement that participant is voluntarily making a decision to participate, or not.
- Statement that he/she has read the form and discussed the information presented.
- Person to contact if problem arises.
- Form must be signed by subject and investigator.
- A copy **must** be given to subject.

# Assent Form

- Similar to consent form.
- To be used with children between age 7 and age 17.
- Should be written at age appropriate level.
- Used in tandem with consent form for parents of participating children.



# Special situations

- Community based research
- On-line and electronic research

# Community-based research

- Away from UGA
- Less day-to-day management by researcher.
- Large numbers of people may be involved.
- Obtaining consent in usual fashion may be difficult.
- Training of community-based personnel may pose problems.

# Community-based research

- These include research protocols conducted in non-campus settings that involve participants from schools, churches, unions, etc.
- Research projects can also reflect "service learning," in which community subjects are encouraged to have input into the conduct of the project.

# Community-based research

- For research taking place in K-12 school settings, researchers must provide to the IRB written approval, on official district or school letterhead, from school administrators (district superintendent or designee, or building principal) documenting that the research projects will minimally impact instructional practices.

# Internet-based research

- Unique opportunities to reach large numbers of subjects.
- Subjects may be more willing to answer questions via the Internet
- Widely used for obtaining survey information.

# Internet-based research

Peculiar problems:

- Obtaining consent.
- Is participant who you think he/she is?
- Are vulnerable populations (i.e. children) posing as adults?
- Do you know the gender, or age, or status, or anything about subject?

# Internet-based research

Ways to obtain informed consent /assent and protecting participants include:

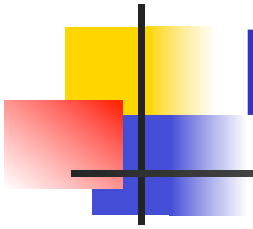
- Setting up a separate URL that contains the required consent/assent form as a front page for study instrumentation and/or interventions.
- This consent/assent page (page 'a') should indicate that by clicking on a link from page 'a' to page 'b', subjects are consenting to participate.
- Page 'a' should also include an e-mail address in addition to a telephone number(s) to withdraw consent and remove data, to the extent possible, upon request of the respondent.

# Internet-based research

- Protocol statement should include information on how email addresses or contact information were obtained, with official permission from third party, if appropriate.
- Email replies should be returned to institutional IT personnel or use a separate CGI-form handler to remove identifying information.

# HIPAA Rules

- HIPAA is the Health Insurance Portability and Accountability Act of 1996
  - Objective of Act is to protect privacy of medical records.
  - Required to be in place on April 14, 2003.



# HIPAA

- Concerned mostly with medical information and is particularly important in clinical trials and in retrospective studies of medical records.
- However, other investigators may record or disseminate information containing medical information such as weight, height, medical problems, etc.

# Conflict of Interest

- Currently a timely topic
- Many faculty have equity interests in companies that may be involved in research.
- Many institutions are taking equity interests in startup companies.

# Conflict of Interest

- Disclosure
  - Check off box on Consent form if there is a real or perceived conflict.
  - UGA has a Conflict of Interest Committee
  - Role of the IRB in conflict of interest situations.
    - If there exists a threat to subjects, the IRB must take a role.

# What's an investigator supposed to do?

- Ethics training
  - Course on the web (CITI training) at Human Subjects Office website
- HIPAA training

# The Human Subjects Office

- provides administrative support for the IRB and is responsible for the review and approval of applications for certain categories or research with human subjects/participants.

# Goals of University Policy

- Comply with:
  - Code of Federal Regulations (CFR) Title 45, Part 46.
  - The basic ethical principles that underlie CFR are summarized in The Belmont Report.
    - These regulations, specifically covering research from grants funded by the National Institutes of Health, have been adopted by UGA to cover all research activities involving human subjects, regardless of source of funding or lack of funding.

# Criteria for IRB Approval

- **minimal risk**
- **potential benefits**
- **equality**
- **safety**
- **privacy**

# Responsibility of Investigators

- Conduct the project as approved by the IRB
- Promptly report any revisions or amendments for review and approval by the IRB prior to commencement of the revised protocol.
- Promptly report any unanticipated problems involving risks to subjects or others to the IRB.
  - Serious: must be reported in writing within 24 hours
  - Others: must be reported in writing within 72 hours
- Request an extension prior to the expiration date if data collection is not complete.
- Notify the Human Subjects Office when data collection is complete.

# Course Directed Human Subjects Activity (HSA)

- In some courses students collect data on human subjects. In some instances, the subjects could be placed at risk.
- proposed HSA should be reviewed and approved prior to initiation of the course work to help ensure that the rights and welfare of human subjects are protected.
  - A faculty member may do this review, or otherwise the review must be conducted by HSO/ IRB. (We' ll do this)

# Student HSA projects that are not submitted to the Human Subjects Office must fall within the parameters

- Ethical Principles for the Protection of Human Subjects
- Understanding of necessary definitions
- Responsibility of Instructors
- Instructor Review of Student Research
- Consent from Participants in Class Projects
- Categories of Research
- Human Subjects Office/IRB Review of Student Human Subjects Activities

# Consent from Participants in Class Projects

**A letter to participants or similar may be needed. The letter may include:**

- Description of the project
- The student's responsibility
- The purpose of this research project
- The participant's actions
- Researcher's actions
- Name of instructor and course

# HSO/IRB Review of Student Human Subjects Activities

- If student HSA involves more than minimal risk or falls outside of the categories, an IRB application must be submitted to and approved by IRB prior to any data collection activity.
- Even if the student research projects fall within the parameters that allow faculty review of the projects, faculty members may have students submit formal IRB applications for review and approval.

# Thank you