

## Human Subjects Protection: Training for Research Teams

Brought to you by:

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### Acknowledgement

- This presentation is a modified version of a tool prepared by the American Academy of Family Physicians National Research Network (AAFP-NRN)
- We gratefully acknowledge their work in creating this resource:
  - Barbara P. Yawn MD MSc, Olmsted Medical Center
  - Wilson D. Pace MD MPH, AAFP-NRN Director
  - Debbie G. Graham MSPH, AAFP-NRN Assoc. Res. Dir.

### Intended Audience

- This session is intended to help physicians, clinicians, physician assistants, nurse practitioners, and office staff understand the key elements of human subjects protection
- This session is *not intended* to replace more detailed instructions and certification required for Principal Investigators and other researchers

### Outline

- History and Ethical Principles
- Institutional Review Boards (IRB's)
- Informed Consent
- Records-Based Research
- Health Insurance Portability and Accountability Act (HIPAA)

## **Section 1.**

### History and Ethical Principles

- Goals:
- Discuss
  - the Tuskegee syphilis "experiment"
  - the National Commission
  - the Nuremberg Code 1947
  - the Beecher article 1966
  - the Belmont report
  - the three basic principles of human subjects protection

### U.S. Public Health Service syphilis “experiment”

- Took place in Macon County, Tuskegee, AL
- The U.S. Public Health Service (PHS) deliberately withheld treatment from poor rural African-American men diagnosed with syphilis
- “experiment” went on from 1932 until negative publicity forced the project to close in 1972
- This led directly to the creation of The National Commission.

### The National Research Act

- the Tuskegee “experiment”:
- Led to the creation of The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. Following this
- Congress passed National Research Act in 1974
  - Title 45 Code of Federal Regulations part 46, **DHHS** Protection of Human Subjects, and
  - Title 21 Code of Federal Regulations part 50, **FDA** Protection of Human Subjects

After WWII Nazi war crimes were investigated and this resulted in the :

### Key elements of The Nuremberg Code 1947 included:

- Experiments with humans must include Voluntary, informed consent is essential
- Experiments must benefit society, and the results must be unobtainable by other means
- Animal testing should precede human experiments
- At all times investigators should Avoid unnecessary physical & mental suffering & injury
- Experiments must be conducted by scientifically qualified persons
- Human subjects may withdraw consent at any time
- Researchers must terminate experiment if injury or death is likely
- An Updated version of this code is included in the Declaration of Helsinki 1964

### Beecher article 1966

- Beecher HK. Ethics and clinical research. N Engl J Med 1966; 274(24): 1354-1360.
- This article brought to the attention of the medical community of the United States that unethical medical research was going on at that time.
- Reviewed 22 examples of questionable ethics in U.S. published research
- This article heightened awareness of problems with unethical clinical research

### Belmont Report

- The National Commission published this report in 1979
- Lays out three basic ethical principles underlying all human subjects research:
- Respect for Persons
- Beneficence
- Justice

<http://ohsr.od.nih.gov/guidelines/belmont.html#gob2>

### Respect for Persons

- Respect for persons incorporates at least two ethical principles:
  - 1. individuals should be treated as autonomous agents
  - 2. persons with diminished autonomy are entitled to additional protections (e.g., children, prisoners, adults with diminished capacity, etc.)
- The extent of protection afforded depends on the risk of harm and the likelihood of benefit
- In human subjects research, respect for persons demands that subjects enter into research voluntarily and with adequate information

### Beneficence

- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being
- In the context of human subjects research, beneficence is understood as an *obligation*
- Two general rules have been formulated as *expressions of beneficence* in this sense:
  - first, do no harm; and
  - maximize possible benefits and minimize possible harms

### Justice

- Who ought to receive the benefits of research and bear its burdens?
- This is a question of justice, in the sense of "fairness in distribution" or "what is deserved"
- Injustice occurs
  - when some benefit to which a person is entitled is denied without good reason; or
  - when some burden is imposed unduly
- Another way of conceiving the principle of justice is that "equals ought to be treated equally"

### Confidentiality Protection

- Pertains to treatment of information disclosed in a relationship of trust with expectation of not being divulged
- Breaches of confidentiality are usually disclosing or transferring information to third parties

### Applying Research Ethics

- Rules to govern investigator-subject relationship
- Informed consent
- Withdrawal of informed consent can be done at any time at subject discretion
- Investigator must be sensitive to positions of power, particularly when you recruit patients of your practice to research.
- Investigators must maintain a moral fiduciary relationship. You are duty bound to provide the best care for your patients and to protect them, even when they are involved in your research projects.

## **Section 2.**

### Institutional Review Board

- Goals:
- Define when a study needs human subjects protection
- Describe researcher's responsibilities
- Issues of subject selection
- IRB composition and role
- Types of IRB Review
- Elements of Continuing IRB Review

### The Research Participant

- An individual from whom a researcher:
- Obtains data through interaction or intervention or
- Obtains identifiable private information
- Who is considered a research subject?
- Patients
- Depending on the nature of the study other's may also be considered a research subject such as:
  - Office staff
  - Clinicians

### Why Do We Need Formal Protections?

- To Promote safety of participants
- To Maintain ethical standards
- To Implement valid research
- To Allay concerns of general public

Who Protects Patients?

- Federal agencies
  - Office for Human Research Protections (OHRP)
  - U.S. Food and Drug Administration (FDA)
- Funding agencies
  - National Institutes of Health (NIH)
  - Agency for Healthcare Research & Quality (AHRQ)
- IRBs, Oversight groups, Data and Safety Monitoring Board (DSMB)
- The researcher

IRB review

- An IRB must review and approve or deem exempt all research involving human subjects
- Primary role is protection of subjects
- There is an ongoing review of continuing research
- These reviews are there to assess adverse events as well as
- Assess protocol violations
- Badly designed research is not worth any risks and will not be approved

An IRB can

- Approve, disapprove or terminate all research activities
- It may Require modifications in protocols as submitted,
- It may Require specific information be given to subjects beyond that required by Federal regulations
- It may also require documentation of informed consent

IRB members

- Composed of at least 5 members who have research expertise
- They are considered to be peers of the Principal Investigator (PI): that is they have similar background & knowledge in subject area
- Also a member of the Public is the member of the IRB.
- May include a Medical ethicist (good, but not required)
- Diversity similar to community in race, ethnicity, and culture

The Research Protocol

- To satisfy the IRB, the Research Protocol must explain:
  - the study in sufficient detail to allow IRB members to judge the scientific merit as well as the risks and benefits
  - It must describe the study population (i.e., subjects)
  - all study interventions (including placebos)
  - It must describe how investigators plan to protect privacy and confidentiality
  - And how they plan to handle data as well as data protection

Types of IRB Review

- Exempt
- Involves minimal risk to subjects
- e.g., non-identifiable data, publicly available data
- Expedited
- non-sensitive topic, no patient contact
- There is either a waiver of consent or previous consent
- e.g., reviewing non-identifiable records
- Full Board Review, where all the board members are convened to review research protocol. This would involve research that covers a sensitive topic, patient contact (never exempt)
- Clinical research, e.g., test of drug efficacy, etc.

Example of Exempt Research

- Sitting in a shopping mall watching the number of people who use cell phones
- Determining timing of physicians arriving at hospital with no identification or knowledge of who they are

Types of IRB Submissions

- Initial submission
- Modification
- Continuous review of all research protocols which is usually annual.

Data and Safety Monitoring Board (DSMB)

- Required for all clinical trials
- Includes 5 to 10 experts in research
- Reviews research data every 6 to 12 months to look for early warning signs of harm and they can stop the study
- The DSMB is Independent of researcher or funding agency

Data and Safety Monitoring Board (DSMB) Should

- Ensure that risks to subjects are minimized and that the research
- Avoids exposure of subjects to excess risk
- Ensure data integrity
- The DSMB can stop a study:
  - if safety concerns arise, or
  - when study objectives have been met

What is an Appropriate Population?

- Women and children must be included whenever appropriate to the research question
- Vulnerable populations must be identified and protected

- Vulnerable populations include:
  - Children
  - Prisoners
  - Pregnant women and fetuses
  - The terminally ill
  - Students/employees
  - Comatose patients
  - Those with diminished capacity to consent

### Can Researchers Pay Subjects To Participate?

- Yes researchers can pay subjects for time & effort
- But the amount of compensation must not be considered a coercive amount. For example:
  - \$5 to answer 15 questions
  - \$15 to complete a 30-minute survey
  - \$100 to complete a panel of questionnaires
  - \$1000 to take a study medication
- High rates of compensation may be considered “coercive”, especially for indigent subjects

### Continuing IRB Review

- Ongoing informed consent
- Adverse event reporting
- Continuing IRB review

### Ongoing Informed Consent

- You as a researcher must inform patients about new options (e.g. new drug or devices) as they become available.
- It is your duty to explain the pros and cons of new drugs or devices versus the study’s drugs and devices to research participants.
- You must give the patient the option to continue study drug or use new drug
- It is the researcher’s responsibility to keep patients informed and up-to-date

### Adverse Event Reporting

- The responsibility of the PI and the study team is to report adverse events to the
  - funding agency
  - Data and Safety Monitoring Board
  - IRB
- May also need to be reported to study participants as directed by DSMB and funder

Continuing IRB Review

- Research projects must be reviewed at least annually
  - IRB will inform the researcher if they require review more often
- As a researcher you must report
- any new forms
- any major changes
- Only emergency changes can be implemented before IRB approval but in almost all cases changes must be approved before they are implemented.

Who is Responsible for Human Subjects Protection?

- More than just the responsibility of the IRB
- It is the responsibility of every person who is involved in the implementation of a study
- It is what you would want for your family member or yourself

**Section 3.**Informed Consent

- Goals:
- What constitutes “informed consent”?
- Elements of Consent
- Special Concerns
  - Language, culture, literacy level
  - Children
  - Proxy consent
  - Waiver of consent
  - Exceptions

What Constitutes Informed Consent?

- Informed consent is a process that involves conveying accurate and relevant information about the study and its purpose. Explaining:
    - Risks
    - Benefits
    - Alternatives
    - Procedures
    - Answering questions from the patient
- ✓ Informed consent is a process; it is not about getting a piece of paper signed. It is about giving the patient enough information to enable them to make an informed decision.



Elements of Consent

- Competent
  - Is the patient competent to provide consent?
- Disclose
  - Is enough information provided to allow an informed decision?
- Comprehend
  - Does the patient truly understand?
- Agree
  - Does the patient freely agree to participate?
- Voluntary
  - Is consent truly voluntary (i.e., free of coercion)?
- Withdraw
  - Does the patient understand that they can withdraw at any time, with no negative consequences to themselves?

Must Consent always be in Writing?

- Not when it might pose a confidentiality risk
- Not when there is minimal risk of harm and involves no procedures that usually require informed consent

Special Concerns

- Language
  - The consent form must be language spoken most easily by the subject
  - Must be literacy appropriate
- Cultural issues
  - In some cultures it is considered rude to ask questions of an investigator or rude to decline what seems to be asked as a favor. Researchers must be aware of these problems.

Children

- It is appropriate to have children from age about 8 to 16 or 18 sign an assent
- This does not replace the parental consent
- Both the child's assent and the parent's consent should be obtained if the child is able to understand the study and to make an informed decision

Waiver of Consent

- When is a waiver of consent appropriate?
  - If the study involves no more than minimal risk
  - If there are no adverse affects to a waiver of consent
  - If the study could not reasonably be done without the waiver
- An "information sheet" may be required for each participating subject
  - Information may also be provided to participants at the completion of the study, if appropriate

### FDA Regulations for Exceptions to Informed Consent

- Life-threatening conditions that meet all of the following:
  - Investigator and another physician believes the situation necessitates the use of a test article
  - Subject or representative cannot consent
  - Insufficient time to obtain consent
  - No alternative available that provides an equal or better chance of survival
- ✓ All of these elements must be in place for an exception of informed consent to be allowed.

## **Section 4.**

### Medical Records Research, HIPAA Issues

- Goals:
- Issues of access for medical records research
- Protect confidentiality of subjects
- Obtain all required approvals before initiation of study

### HIPAA (The Health Insurance Portability and Accountability Act) includes a (Final Privacy Rule)

- This includes an authorization to view Protected Health Information (PHI) in medical records
- It is important as a researcher to understand that authorization for disclosure of PHI is different from Consent for Research
- Authorization may be incorporated into Consent Form or researchers may use 2 separate forms (depending on IRB requirement)
- One for the research subject to consent to the study and the second for the research subject to give authorization for the researcher to view or access PHI.
- Waiver of authorization may be possible but only through the IRB.
- Compliance to the HIPAA rule is the key to protecting the Confidentiality and Privacy of your patients.

### Risks of Medical Records based Research

- Placing the subject at risk of criminal or civil liability if their private information is revealed.
- It could damage the subject's financial standing, employability or reputation
- It could damage a company or other entity

### Privacy Concerns

- Protecting the individual’s privacy is an example for “Respect for Persons”
- There are very strict rules about data collection and data management
- Keep records secure (e.g., locked cabinet)
- Remove identifying and linking information as soon as possible
- You must be aware of applicable state laws

## **Summary**

### History and Ethical Principles

- Tuskegee syphilis “experiment”
- National Commission
- for the Protection of Human Subjects in Biomedical and Behavioral Research
- Belmont Report
- Principles of Respect for Persons, Beneficence, and Justice
- Beecher article
- awareness of unethical research

### Institutional Review Boards

- Exempt
  - minimal risk to subjects
  - e.g., non-identifiable data, publicly available data
- Expedited
  - non-sensitive topic, no patient contact
  - waiver of consent, previous consent
  - e.g., using non-identifiable records
- Full Board Review
  - sensitive topic, patient contact (never exempt)
  - Clinical research, e.g., test of drug efficacy, etc.

### Informed Consent

- Withdraw: subjects may choose to withdraw at any time
- Proxy consent: may need proxy consent from authorized patient caregiver
- Emergency exceptions: another physician must agree that emergency consent conditions apply
- Ongoing IRB review: “Respect for Persons” requires subjects be informed if a new drug/device is available (i.e., a viable alternative to the study drug/device)

Summary: Medical Records Research, HIPAA issues

- Consent to research project is not the same as consent to use or access Protected Health Information (PHI)
- In the absence of patient authorization, a waiver of the HIPAA requirement must be obtained from IRB if medical records are reviewed for research purposes
- Additional Resources
- Office for Human Research Protections
- <http://www.hhs.gov/ohrp/education/>
- Collaborative Institutional Training Initiative (CITI)
- <http://www.citiprogram.org/>
- National Cancer Institute
- Protecting Human Research Participants
- <http://phrp.nihtraining.com/users/login.php>

# Human Subjects Protection Quiz for STARNet Members

## 1. Human Subjects Protection Training

In order for you to begin an IRB approved research project with STARNet, you are required to complete this Human Subjects Protection Training course by watching a 30 minute video presentation and passing this 14 question quiz with an 80% or better.

Each question has a link that will allow you to review relevant sections of the Human Subjects Protection training in outline format.

Please contact the STARNet Coordinator Marisa Rodriguez with any questions you may have at 210-567-7892

### 1. Completing this survey is one of the requirements for STARNet (South Texas Ambulatory Research Network) membership.

Name:	<input type="text"/>
Company:	<input type="text"/>
Address:	<input type="text"/>
Address 2:	<input type="text"/>
City/Town:	<input type="text"/>
State:	<input type="text" value="6"/>
ZIP/Postal Code:	<input type="text"/>
Email Address:	<input type="text"/>
Phone Number:	<input type="text"/>

### 2. Which of the following lists the three principles discussed in the Belmont Report?

[Click here to review Section 1. History and Ethical Principles](#)

- Informed Consent, Institutional Assurance, Researcher responsibility
- Respect for Person, Beneficence, Justice
- IRB Review, federal regulations, Declaration of Helsinki
- Privacy, Confidentiality, Equitable selection of subjects

### 3. In what way did the Beecher article impact research in the United States?

[Click here to review Section 1. History and Ethical Principles](#)

- It heightened awareness of problems with unethical research.
- It resulted in the creation of the IRB.
- It reinterpreted the Belmont principles with a focus on therapeutic medical research.
- It prompted Congress to create an ad hoc panel to provide oversight for human research.

## Human Subjects Protection Quiz for STARNet Members

**4. An investigator wishes to study lifestyle and diet influences on the risk of developing a specific cancer. The investigator chooses a case-control design with paired lifestyle interviews and a few blood and urine tests and assigns a study manager to identify patients with the diagnosis from the pathology logbook that lists names. The study manager would then ask each patient's primary physician for permission to contact the patient. Which of the following is required before the investigator begins the study?**

**[Click here to review Section 2. Institutional Review Board](#)**

- A Clinical trials office
- Hospital accreditation
- Permission from the Oncology Department
- IRB review and approval

**5. Which of the following studies led to the establishment of the National Research Act and ultimately the Belmont Report and Federal regulations for human subject protection?**

**[Click here to review Section 1. History and Ethical Principles](#)**

- Nazi medical experiments
- Jewish chronic disease study
- obedience to authority study (Milgrim study)
- The Public Health Service (PHS) syphilis study

**6. An investigator fails to inform subjects about the foreseeable risks in a study of a new drug. Which of the following best describes the ethical principle violated?**

**[Click here to review Section 1. History and Ethical Principles](#)**

- Justice
- Respect for persons
- Research integrity
- Access to research

## Human Subjects Protection Quiz for STARNet Members

**7. As part of its commitment to evidence-based medicine, Medical School Alpha wants to ensure that its students and residents will be able to understand and evaluate the results of future research. Accordingly, the school requires each student and resident to develop a research protocol, collect data on living and deceased patients, analyze the data and report the results. Many of these studies will involve medical record or chart reviews, although patients have never explicitly agreed to have their medical records used this way. Does the Final Privacy Rule make these chart reviews improper without further IRB or Privacy Board action? Consider each of the answers and choose the most appropriate on.**

[Click here to review Section 4. Medical Records Research, HIPPA Issues](#)

No, because patients will be given a notice of privacy practice when admitted to the Medical School Alpha which clarifies information can be collected for future use in research.

No, because the patient information cannot be traced to anyone and therefore is "de-identified" as required by the Final Privacy Rule.

No, although the patients never authorized this use of their health care data, a waiver of consent for chart review approved by the IRB would be sufficient for the research to proceed.

Yes, the IRB or Privacy Board must grant a HIPAA compliant waiver of authorization for this undertaking because the research is not authorized by a patient, not a review preparatory to research and does not solely use decedent information.

**8. A consent for research under the Common Rule is the same as an authorization for disclosure of PHI under the Final Privacy Rule.**

[Click here to review Section 4. Medical Records Research, HIPPA Issues](#)

True

False

## Human Subjects Protection Quiz for STARNet Members

**9. An elderly man recently diagnosed with lung cancer is screened for a clinical trial using a new investigational drug. The investigator has carefully explained all of the required information about the study to the subject and the subject's daughter. The subject demonstrates his understanding and willingness to participate, but is not able to sign the informed consent document due to paralysis from a swimming accident years before. The subject's wife is his legally authorized representative, but she is out of town on a business trip. Which of the following is the most appropriate action to take for the investigator?**

**[Click here to review Section 3. Informed Consent](#)**

- Request that the IRB waive the requirement for a signed informed consent.
- The investigator can go ahead and treat the man without a signed consent since he verbally agreed to participate.
- Exclude the man from the study.
- Send a copy of the informed consent via facsimile to the subject's wife. After she has had the opportunity to speak to the investigator and her husband, she can sign the informed consent and fax it back.

**10. A general requirement for the informed consent is that no informed consent may include any exculpatory language. Exculpatory language is that which waives or appears to waive any of the subject's legal rights or releases or appears to release those conducting the research from liability for negligence. Which of the following statements in a consent form is an example of exculpatory language?**

**[Click here to review examples of exculpatory language](#)**

- In the event of any injury you may have related to this research, you will be given medical treatment.
- The investigator may stop you from participating in this research without your consent if you experience side effects that make your condition worse. If you become ill during the research, you may drop out.
- Your participation in this research is voluntary. If you choose not to participate, or change your mind later, your decision will not affect your relationship with your doctor or your right to health care or other services that you may be eligible for.
- You must provide blood samples that will be kept in a "bank" for future research. Once you have provided these blood samples, you cannot change your mind about being in the research and have the sample removed from the "bank."



## Human Subjects Protection Quiz for STARNet Members

**11. An investigator is confronted with a life-threatening situation that necessitates using a test article in a human subject who is unable to provide informed consent and there is no time to obtain consent for the individual's legal representative. Under the FDA regulations for using test articles, which of the following describes the best course of action for the investigator.**

[Click here to review Section 3. Informed Consent](#)

- Do not use the test article until either the subject or the subject's legal representative can give consent.
- Submit a research protocol to the IRB and justify an expedited review approval of the consent document so test article can be used immediately.
- Use the test article without obtaining consent from the subject or the legal representative then notify the IRB.
- The investigator and another physician agree that the situation necessitates the use of the test article. An exception or waiver for informed consent can be made under these circumstances. The IRB will be notified later.

**12. A 46-year-old man is currently enrolled in a Phase I study of a drug for severe diabetic neuropathy. While the study is on going, a new drug becomes commercially available that may have equal or greater benefit to the subject. The investigator should do which of the following?**

[Click here to review Section 2. Institutional Review Board](#)

- Tell the subject about the new drug but discourage him from switching treatments until the study is completed.
- Withhold this new information to avoid confusing the subject with other treatment options or alternatives.
- Give the subject comprehensive information about the new drug, including its side effects. Discuss the pros and cons of both the investigational drug and the commercially available drug and then allow the subject to decide whether to withdraw from the research to take the new drug.
- Do not tell the subject about the new drug since physicians have the right to try out new treatments with their patients.

**13. Part of the IRB's charge is to protect "vulnerable populations." Which of the following groups would be considered part of a "vulnerable population."**

[Click here to review Section 2. Institutional Review Board](#)

- Children
- Prisoners
- Pregnant women and fetuses
- Students/employees
- All of the above

## Human Subjects Protection Quiz for STARNet Members

14. The IRB offers 3 levels of review: Exempt, Expedited, and Full Review. Which of the following is an example of a study that could qualify for "exempt" status with the IRB?

[Click here to review Section 2. Institutional Review Board](#)

Research involving NON-IDENTIFIABLE data or publicly available data.

Research involving a sensitive topic such as HIV or drug abuse.

Research evaluating the efficacy of new cancer drugs.

Research testing alternative patient interventions for diabetes.

# Human Subjects Protection Quiz for STARNet Members

## 2. Thank you so much for your interest in STARNet.

You will be emailed soon by STARNet Coordinator, Marisa F. Rodriguez, about the results of your quiz.

If you have any questions please don't hesitate to call the PBRN Resource Center at (210) 567-7892 or email Marisa Rodriguez at [rodriguez21@uthscsa.edu](mailto:rodriguez21@uthscsa.edu)