**REQUIRED MODULES FOR BIOMEDICAL RESEARCH INVESTIGATORS**

**History and Ethics of Human Subjects Research**

* The Nuremberg Code (1947) included the requirement of the voluntary consent of subjects.
* The death of a research subject (Jesse Gelsinger) was what received public attention to the problems within the IRB system.
* The use of prisoners in research is a concern under the Belmont principle of Justice because: The Belmont Principle of Justice requires the equitable distribution of both the benefits and burdens of research. Prisoners should not bear the burden of participating in research that only benefits the larger society.
* The primary result of the Beecher article was to expose ethical abuses occurring in research involving human subjects in the US, well after the revelations about research by the Nazi regime.
* The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The identification of guidelines, ethical principles and regulations came as a result of the deliberations of the National Commission.
* Informed Consent is considered an application of the Belmont principle because respect for persons involves respecting individual autonomy in the decision to participate in research. That respect is implemented through the process of informed consent.
* Issued in 1974, 45 CFR 46 raised to regulatory status the US Public Health Service policy of 1966 "Clinical research and investigation involving human beings”.

**Basic Institutional Review Board (IRB) Regulations and Review Process**

* A subject in a clinical research trial experiences a serious, unanticipated adverse drug experience. The most appropriate action for the investigator to take is to report the adverse drug experience in a timely manner using the forms provided by the institution.
* Research investigators are responsible for retaining signed consent documents, IRB correspondence, and research records for at least three years after completion of the research. Because research records are the property of the institution, local institutional policy or sponsoring agency requirements may dictate these records are kept longer. The sponsor and the IRB office should be contacted to make sure that the minimum of three years meets their requirements
* The study involves no more than minimal risk and meets one of the allowable categories of expedited review specified in federal regulations. Expedited review procedures are appropriate only for protocols that present no greater than "minimal risk" to subjects and involve only procedures included in federally specified categories. Population considerations, such as healthy volunteers, are only relevant insofar as they affect the assessment of risk. The IRB may not conduct an expedited review for the convenience of either the IRB or a student researcher, if the protocol is otherwise not eligible.
* Amendments involving changes to IRB-approved protocols do NOT need prior IRB approval if The changes must be immediately implemented for the health and well-being of the subject. All amendments involving changes to IRB-approved protocols must be reviewed and approved in advance of implementation, unless changes must be put in place immediately to respond to an unexpected risk or problem arising during the course of a study.
* IRB continuing review of a greater than minimal risk approved protocol that is currently enrolling subjects must be reviewed at least annually, although IRBs may specify a shorter review period. It is the responsibility of the principal investigator to hold signed consent forms in confidentiality. Copies of these forms are not required by federal regulation to be reviewed by the IRB. Please note, however, that an institution's local policy may require copies of signed consent forms as part of the IRB continuing review process.

**Informed Consent**

* The purpose of the Informed Consent process is to ensure human research subjects are provided all of the information necessary to make informed choices about participating in research.

“An elderly gentleman, whose wife is his legally authorized representative (LAR) since his strokes several years ago, was recently diagnosed with lung cancer. He is eligible for a clinical trial using a new investigational drug that aims to treat lung cancer. He is able to express interest, shows a basic understanding of the nature of the trial, and gives his assent to participation. The subject's wife is out of town on a business trip.”

* The IRB will not provide a waiver of consent under these circumstances and the man should not be excluded from the study simply because his legally authorized representative is temporarily unavailable to sign in person. Verbal approval does not satisfy the FDA requirement at 21 CFR 56.109(c) of signed informed consent document. When obtaining consent from a legally authorized representative (LAR) who is not able to provide signed consent in person, it is acceptable to send the informed consent document to the LAR by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it is discussed as noted in the FDA's FAQs. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical investigator by facsimile.

“A 46-year-old man is currently enrolled in a Phase 2 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?”

* Phase 2 clinical trials involve volunteers who have the disease or condition to be treated. These trials help physicians and researchers begin to learn more about the safety of the new drug treatment and how well the drug treats the targeted disease or condition. Several different doses of the drug may be tested to see which dose has the desired effects. Subjects are monitored for side effects and for any improvement in their illness, symptoms, or both. Informed consent is not a one-time procedure but a continuing and ongoing process. 45 CFR 116(b) and 21 CFR 50.25(b) require that the Informed Consent document include a statement indicating that if significant new findings are developed during research which may relate to the subject's willingness to continue they will be explained to the subject. The Informed Consent document must also describe the process whereby subjects will be notified of significant new findings.

“A general requirement for the informed consent form is that it may not 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?”

* Exculpatory language is written content in the consent document through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. Such language is specifically prohibited.

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 from the individual’s LAR and no alternative method or recognized therapy is available. Under the FDA regulations for using test articles, which of the following describes the best course of action for the investigator:

* The life- threatening situation requires a timely decision so that the test article can be ethically used. It would be unethical to withhold emergency treatment until a research protocol is submitted and approved by the IRB. Not using the test article in a situation where it might save a life is also unethical. The Federal regulations (21 CFR 50.24) provide the option of using the test article in a life-threatening condition involving an individual subject where the following requirements for an exception from informed consent are met. 1. The investigator, with the concurrence of another physician, believes the situation necessitates the use of a test article (i.e., an investigational drug, device, or biologic). 2. The subject and/or legally authorized representative is unable to communicate consent. 3. There is insufficient time to obtain consent. And 4. No alternative exists that will provide an equal or better chance of saving the subject's life.

**Social and Behavioral Research (SBR) for Biomedical Researchers**

“A researcher is conducting a written survey about people's attitudes toward walking as an exercise option at the local shopping mall that supports a walking program. The survey is anonymous (without codes, names, or other information) and subjects may complete the survey and place it in a box at the shopping mall exits. Which of the following is the most important issue that the researcher addressed in planning the research?”

* The most important issue that the researcher addressed in planning the research is the confidentiality of the individual subject's responses. By making the survey anonymous, no one, even the researcher, has knowledge of the individual's identity. While recruitment strategies, minimizing emotional distress, and having a large sample size are important issues to address, the confidentiality of the individual subject responses is the most important in this example.

“A researcher wants to invite therapists to participate in small focus groups to discuss their perceptions regarding "troubled" adolescent girls and the relationships they have with their parents. Specific clients of the therapists will not be discussed. Which of the following will be the most important issue for the researcher to consider when planning the research?”

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| * Most risks of harm from SBR research results from invasion of privacy and breaches of confidentiality. Researchers should design strategies to minimize the possibility of breaches of confidentiality and inform all subjects about the potential for these breaches especially in a focus group situation. While emotional distress, compensation and recruiting strategies are all important issues for the researcher to consider in this situation, the potential for breach of confidentiality is the most important. |

“Which of the following most accurately describes the risks associated with SBR?”

* It is more difficult to predict how individuals will react to questions and situations in which their behavior is observed or manipulated than to physical data collection methods such as blood draws. The reactions may be of considerable duration. Once those reactions happen, they may be difficult to assess, serious enough to require treatment and may even be untreatable compared to treating physical harms.

“Which of the following is considered a SBR data collection method?”

* Hearing screenings, blood draws, and other physical exams are usually designed to collect physiological data, not information about attitudes and beliefs. Interviews are designed to collect information about attitudes, beliefs, and behavior and are data collection methods typically used by SBR researchers.

**Records-Based Research**

**“**An investigator obtains consent and HIPAA authorization from subjects to review their medical records and HIV status. He plans to go back to the medical record, so the HIV status information is stored along with subject identifiers in a database that he keeps on his laptop computer. His laptop is stolen. This incident constitutes:”

* Privacy is about people and their expectations. Privacy risk pertains primarily to the methods used to obtain information about subjects. Confidentiality pertains to the actual treatment of the personal information once it is obtained. In other words, now that the researcher has obtained private information, how will it be used, stored, and reported. Clearly, this event represents a breach of confidentiality.

“A researcher wants to conduct a secondary analysis using a Centers for Disease Control and Prevention (CDC) database that was collected by the agency solely for surveillance purposes from 1996-2006. The researcher did not participate in the initial collection of the data. The database is publicly available. The database does not include any identifiers. The IRB makes a determination that the individuals whose records will be reviewed do not meet the federal definition of human subjects.”

* Records-based research activities may not meet the federal definition of “human subjects” research. A human subject is “a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (Protection of Human Subjects 2017). In this case, the investigator did not collect the data directly from the human subject and the investigator cannot readily ascertain the identity of the subject; therefore, this would not qualify as human subject research.

“In order to grant a waiver or alteration of the requirements of informed consent, an IRB must find which of the following:”

In order for an IRB to grant a waiver of consent, it must ensure the following federal criteria at 45 CFR 46.116 are met:

* The research involves no more than minimal risk to the subjects;
* The research could not practicably be carried out without the requested waiver or alteration;
* If the research involves using identifiable private information, the research could not practicably be carried out without using such information in an identifiable format;
* The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
* Whenever appropriate, the subjects (or legally authorized representatives) will be provided with pertinent information after participation.

**Genetic Research in Human Populations**

“Investigator A conducts research on emphysema using biospecimens from human subjects. The consent form indicates that the research will focus exclusively on emphysema. Investigator B wishes to use the biospecimens for research on lung cancer. Can Investigator B use the specimens for cancer research without re-consent if the specimens are de-identified?”

* Under the regulations, research with de-identified specimens is not considered human subjects research. However, many commentators consider it ethically problematic to use specimens in a manner that is not consistent with the language in the informed consent document.

“Which choice is the best definition of “genetic determinism?””

* Genetic determinism is the notion that genes have a controlling influence on human health, behavior and disease. However, current thinking is that genes function in a complex relationship with environmental influences, meaning that genes alone are not determinative.

“Which of the following statements is accurate in determining subject risk involved in a genetic study:”

* Genetic research covers a broad spectrum of research from surveys and chart reviews to gene transfer studies. Therefore no assumptions should be made about risk in genetic research – each study must be evaluated on its own merits.

“As of January 2015, the NIH expects investigators to obtain the informed (valid) consent of research participants in NIH -funded genetic research for broad research use of data and data sharing, even if the cell lines or specimens are:”

* The new NIH policy expects informed (valid) consent even when the source individuals for genetic data are not identifiable (de-identified) to investigators accessing and using the data.

Which choice best describes the purpose of most pharmacogenomic research?

* Pharmacogenomics has broad goals to understand the relationship between individual genotypes and individual response to drugs in terms of safety and efficacy. This knowledge may reduce cost but that is not the primary purpose of this research.

Identify which types of discrimination the Genetic Information Non-Discrimination Act (GINA) protects individuals from:

* GINA protects individuals against discrimination in health insurance and employment. Other forms of discrimination are not addressed by GINA.

# Populations in Research Requiring Additional Considerations and/or Protections

“When an IRB is reviewing a research study and they are considering if a potential subject population is vulnerable, they should consider:”

* IRBs should assess if there is a power differential and if it would affect the potential subjects, making them vulnerable to coercion. According to the module authors, it is important for IRBs to ask researchers to fully describe the population to be studied and the situations in which the potential research subjects find themselves. This should answer both the question about the intrinsic factors or attributes as well as the situational forces that may give rise to different types of vulnerability. The other responses should also be considered by the IRB during their review of the research, but do not relate to identifying if the subject population is vulnerable.

“Which is true of inducements in research?”

* Inducements are offers that influence people to make decisions, or do things they would not otherwise do. Inducements and the influence they cause may be acceptable, or they may be “undue,” and the distinction is not always clear or universally agreed upon. Offering $10 may be acceptable for an hour-long research study; offering $1000, or a better grade in a class, is probably not appropriate. In general, inducements constitute an “undue influence” if they alter a potential subjects decision-making processes such that they do not appropriately consider the risk-benefit relationship of the research.

“A subject participates in a drug study because treatment is available at no or reduced cost, and he could not otherwise afford it. This is an example of:”

* Economic vulnerability arises when prospective subjects are disadvantaged in the distribution of social goods and services (income, housing, or healthcare). Participation in research offers the possibility of payment or attainment of healthcare or other services that are otherwise not available, and induce persons to enroll in a research study when it might be against their better judgment and when otherwise they would not do so. These inducements to enroll threaten the voluntary nature of consent and raise the danger of exploitation.
* Prospective subjects who belong to undervalued social groups may be subject to social vulnerability. The perception of these groups as less valuable to society could lead to reduced concern (by researchers) for risks of harm and burdens on those groups, and increase the risk of exploitation. Prospective subjects in research who are subject to the formal authority of others may have an institutional vulnerability. These individuals have the cognitive capacity to consent but may not be able to make a truly voluntary choice, and may be unduly influenced (or coerced) to participate when they otherwise might not have done so. Prospective research subjects who are not able to comprehend information, deliberate, and make decisions about participation in a proposed research study have a cognitive or communicative vulnerability.

“According to the authors, there are four common abuses that historically are described as giving rise to vulnerability. Which response below contains the correct four?”

* There are four common abuses that historically are described as giving rise to vulnerability 1) physical control, 2) coercion, 3) undue influence, and 4) manipulation. These exist along a continuum of severity with physical control being the most severe and undue influence and manipulation being the least (Nelson and Merz 2002, V69-80). The other abuses– prejudice, neglect, and disrespect – should still be avoided in research.

“Which is an example of a situation where deferential vulnerability might be a factor?”

* In deferential vulnerability, the authority over the prospective subject is due to informal power relationships rather than formal hierarchies. The power relationship may be based on gender, race, or class inequalities, or they can be inequalities in knowledge (such as, in the doctor-patient relationship). Like institutional vulnerability, deferential vulnerability increases the risk of harm that informed consent would be compromised because it is not fully voluntary.

“Subjects with a serious illness may be at risk for exploitation because they may be desperate for a possible cure. This is an example of:”

* Medical vulnerability arises when prospective subjects have serious health conditions for which there are no satisfactory standard treatments. Subjects with serious health problems may not be able to adequately weigh the risks and potential benefits of the research. Subjects are at risk of exploitation because they may overestimate potential benefit. Deferential vulnerability is similar to institutional vulnerability, but the authority over the prospective subject is due to informal power relationships rather than formal hierarchies. Economic vulnerability arises when prospective subjects are disadvantaged in the distribution of social goods and services (income, housing, or healthcare). Therapeutic misconception occurs when subjects blur the roles played by physician-researchers and fail to appreciate the difference between research and treatment.

“Identify the following groups that are protected in the federal regulations (45 CFR 46), specifically in Subparts B, C, and D with additional protections:”

The HHS federal regulations at 45 CFR 46 includes three subparts (B, C, and D) that specifically provide additional protections to vulnerable groups. The vulnerable groups identified are:

* 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 as Subjects
* Subpart D. Additional Protections for Children Involved as Subjects in Research.
* The regulations do not provide specific additional protections for elderly, mentally disabled or terminally ill.

“In considering NBAC’s analytic approach, an otherwise competent person who is acutely ill might be considered at especially high risk of harm for:”

* Subjects who do not lack capacity, but are in situations that do not allow them to exercise their capacities effectively, may suffer situational cognitive vulnerability. This might occur when a subject is distracted or during an emergency situation, such as an acute illness or injury. Capacity-related cognitive vulnerability can occur when subjects to some extent lack capacity to make informed choices. Communicative vulnerability can occur when subjects do not lack capacity, but due to limited ability to communicate with the researchers are not able to exercise their capacities effectively. Economic vulnerability arises when prospective subjects are disadvantaged in the distribution of social goods and services (income, housing, or healthcare).

“The NBAC looks at characteristics individuals might have that would prevent them from being able to provide voluntary informed consent. The traits may be thought of as falling into six broad areas: cognitive or communicative, institutional, deferential, medical, economic, and social. Prospective research subjects who are not able to comprehend information, deliberate, and make decisions about participation in a proposed research study have a:”

* Prospective research subjects who are not able to comprehend information, deliberate, and make decisions about participation in a proposed research study have a cognitive or communicative vulnerability.

**Research involving children**

“A federally funded research study involving children 8 to 12 years old involves collecting a single voided urine sample to assess the frequency of asymptomatic proteinuria (higher amounts of protein in the urine without any signs or symptoms of illness or infection). Your IRB has determined that assent of children age 8 and older is required for the study. A 10-year-old firmly declined to participate in the study described above. Which of the following procedures best describes the action to be taken by the investigator?”

* The assent of minors to participate in research is required, unless the "capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well being of the children and is available only in the context of the research" (45 CFR 46.408). The IRB determined that an 8 year old was capable of providing assent for participation in this study, and in this situation, the child's decision cannot be overruled by the permission of one or both parents.

“A federally funded research study involving children 8 to 12 years old involves collecting a single voided urine sample to assess the frequency of asymptomatic proteinuria (higher amounts of protein in the urine without any signs or symptoms of illness or infection). According to 45 CFR 46, an IRB's risk assessment would likely conclude that this study involves:”

* 45 CFR 46.102(i) defines minimal risk as the "probability and 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." Because the risk associated with collection of a single voided urine specimen is not greater than risks encountered in the course of a routine physical examination, this research constitutes "minimal risk."

“An investigator proposes a study to determine the clinical relevance of a new assay technique to measure minimal residual disease (MRD) in adolescent (age 14-16) cancer patients undergoing chemotherapy. The study requires that two additional bone marrow aspirates be performed during the course of chemotherapy. The subject's chemotherapy will not be altered based on the results of the assay technique measures. However, future patients with cancer would benefit from improved interventions based on study findings. The IRB determined that the activity was a minor increase over minimal risk. Which of the following statements best describes the IRB approval requirements for involving adolescent cancer patients in the research study?”

* The research, as described presents greater than minimal risk and no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition. It is therefore potentially approvable under 45.406, provided: (1) the risk represents a minor increase over minimal risk; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

# FDA-Regulated Research

A sponsor proposes research to evaluate reengineering a commercially available pacemaker. It is hoped that the new pacemaker will pose fewer risks to individuals when compared to the current commercially available product. How should this device be classified?

* A significant risk device presents a potential for serious risk to the health, safety, or welfare of the subject and it: (1) Is intended to be implanted into a human; (2) Is used in supporting or sustaining human life; (3) Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or (4) Otherwise presents serious risk to health, safety, and welfare of a subject.

An adult with attention deficit hyperactivity disorder (ADHD) presents to a physician. To date, no behavioral or drug interventions have proven useful. The physician has just read several reports about a drug that is approved and marketed for another indication, but has shown some benefit for ADHD. The physician wants to prescribe this drug, in the labeled marketed dose, for the individual patient. Which of the following would be the most appropriate course of action?

* Based on physician's best medical judgment the patient may be treated with the drug since it is a marketed drug with an approved labeled dosage. An IND is not required. There is no research being conducted for the purpose of changing the labeling of the drug or marketing a new indication.

An investigator proposes to study a marketed product sold to treat high blood pressure in individuals over age 12 using a liquid formulation for children under age 12. The drug sponsor hopes that the information from the research can be used to change the labeling for use of the drug in younger children. Which of the following is the investigator's most appropriate course of action?

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| * An IND is required. The investigator and the sponsor are proposing research that may change the formulation of the drug, the dosage, and the population (children) from the currently approved labeling for this drug. An IDE is not required as there is no device involved. Because this research is on drugs, it is under the primary purview of, and regulated by the FDA, not OHRP. |

The FDA's regulations related to electronic records and electronic signatures (21 CFR Part 11) are intended to:

* 21 CFR Part 11 Electronic Records; Electronic Signatures; Final Rule, often referred to as Part 11, was published May 20, 1997 and was intended to enable, but not require, the use of electronic documents in the regulatory process for drugs and devices. Part 11 specifies processes that must be in place assuring that electronic documents and signatures are equivalent to paper documents and handwritten signatures.

An academic medical center is selecting a new database system for clinical research. The system needs to be "Part 11 compliant" in order to allow:

* Part 11 specifies processes that must be in place assuring that electronic documents and signatures are equivalent to paper documents and handwritten signatures. Therefore, if an institution wants to eliminate all paper records for research, the electronic system must be "Part 11 compliant."

# Recognizing and Reporting Unanticipated Problems Involving Risks to Subjects or Others in Biomedical Research

# “A Data Safety Monitoring Board report for an investigator-initiated investigational drug study indicates a significantly higher than anticipated rate of an expected adverse event. This event required revision of the informed consent form to disclose the higher rate. A change in the eligibility criteria of the protocol to reduce the risk was implemented. Current subjects would be reconsented.”

* This is an unanticipated problem because the actual rate for the adverse event was significantly higher than expected, placing subjects at increased risk. The IRB should be notified of all unanticipated problems. Subjects should always be reconsented when there is a significant change in risk, which may affect their willingness to continue in the study. Depending on the funding of the study, OHRP must be notified. Because the study falls under the FDA regulations, FDA must be notified.

“An investigational biologic administered to the first two subjects in a Phase II clinical trial was not appropriately screened for two viral contaminants, HIV and Hepatitis B, due to human error in the screening process. Follow-up testing indicated that the subjects and their partners were not infected. The subjects and others were notified of the increased risk.”

* This is an unanticipated problem because the screening procedure problem was not anticipated; both the subject and others were exposed to risk and could have been infected with Hepatitis B or HIV. A Phase II clinical trial involving a biologic falls under the jurisdiction of the FDA.

A study requires that each subject be given two study drugs. The first study drug is given on Day 1. A second study drug is given on Day 7 to counteract the toxicity of Drug 1. Subject # 4-706 is given Drug 1 on Day 1. Due to a snowstorm, Subject 4-706 is delayed for several days before returning to the site for Drug 2. Missing the administration of Drug 2 on Day 7 placed the subject at risk of significant toxicity. This event required the subject be notified of the increased risk and required close monitoring of the subject by phone.

* This is an Unanticipated Problem that does not include an Adverse Event. The possible delay in administration of Drug 2 was not anticipated, the possible toxic reaction was related to participation in the research and the delay in administration of Drug 2 resulted in an increase in possible harm to the subject. In this case, the subject was monitored, but there is no indication that a toxic reaction occurred. The FDA should be notified.

“A subject received the wrong study drug resulting in severe nausea and vomiting, and a visit to the emergency room for treatment. The subject notified the study coordinator the day after the emergency room visit. The study coordinator reviewed the subject’s study records and discovered the error. The coordinator notified the subject of the study drug error, which caused the nausea and vomiting. The investigator notified the IRB and the IRB approved a revision of the standard pharmacy procedure for administering investigational drugs”

* Receiving the wrong study drug is an unanticipated problem because all the criteria for an unanticipated problem are met. This subject required medical treatment suggesting the increased risk was serious. This event is also an adverse event because the subject required medical treatment. The IRB was properly notified and approved a change in pharmacy procedures to increase subject safety. The FDA must be notified.

“Housekeeping employees of the medical center were recruited for a federally funded study of blood pressure, blood count levels, infectious disease history, and job stress. The interviews and blood tests were conducted in a private location not affiliated with the study center. Follow-up interviews were conducted in the same location. The study coordinator stopped at the cafeteria on her way back to the study office after the second study visit for the last three study subjects and lost the three file folders. Records of one subject indicated he had a history of a sexually transmitted disease and another had recently been treated for tuberculosis. The subjects were notified of the loss. Following this event, the IRB approved a protocol change requiring that all records be transmitted electronically to the study office using the medical center’s secure network.”

* Regardless of the type of study, when subjects’ research records containing protected health information (PHI) are lost, the event is considered an unanticipated problem. This event required the subjects be notified of the increased risk, and required a change in the way data were stored and protected. This is not an adverse event because there was no medical occurrence involved. OHRP should be notified.

**Research and HIPAA Privacy Protections**

“HIPAA includes in its definition of “research,” activities related to:”

* Like the Common Rule, HIPAA defines research as a “systematic investigation, including research development, testing, and evaluation, designed to develop and contribute to generalizable knowledge” (Protection of Human Subjects 2018; Security and Privacy 2013).

HIPAA protects a category of information known as protected health information (PHI). PHI covered under HIPAA includes:

* HIPAA’s protections reach only a subset of individually identifiable health information – formally called protected health information or simply “PHI” – created in or by what HIPAA calls covered entities. Covered entities include individual health providers, health provider organizations, health plans, and health information clearinghouses that engage in electronic healthcare transactions. (See Health and Human Services Covered Entity Decision Charts.) HIPAA’s protections for PHI extend to non-U.S. citizens’ information as well.

A covered entity may use or disclose PHI without an authorization, or documentation of a waiver or an alteration of authorization, for all of the following EXCEPT:

* If the data in question meet the definition of PHI and are being used for purposes that fall within HIPAA’s definition of research, HIPAA generally requires explicit written authorization (consent) from the data subject for research uses. However, HIPAA provides several alternatives that can bypass such authorizations:The research involves only minimal risk.

1. The research is used solely for activities preparatory to research.
2. Only deceased persons' information is used.
3. Only de-identified data is used.
4. Only a “limited data set” is used, under an approved “data use agreement.”
5. It is research where all legal permissions were in place before HIPAA took effect.

HIPAA’s protections for health information used for research purposes…

* HIPAA's relatively new data-focused protections, which took effect starting in 2003, supplement Common Rule and FDA protections; they are not a replacement. Institutional Review Board (IRB) protocol reviews using Common Rule and FDA criteria remain as before, including aspects related to data protection. IRBs may have the responsibility for addressing HIPAA's additional requirements in their reviews when those apply; or some responsibilities may be given to another kind of body that HIPAA permits (a Privacy Board) or to an institutional official that HIPAA requires (a privacy officer). These federal standards complement states’ and accreditation bodies’ requirements.

A HIPAA authorization has which of the following characteristics:

* Authorizations are required unless the proposed use meets one of the exceptions listed in the HIPAA regulation. It is never at the researcher's discretion. When they are required, authorizations must be: In "plain language" so that individuals can understand the information contained in the form, and thus able to make an informed decision. Executed in writing, and signed by the research subject (or an authorized personal representative). Authorizations must include a specific description of the PHI to be used or disclosed, the name(s) or other identification of persons involved in the research, and description of each purpose of the requested use or disclosure. Authorizations can be combined with other documents and can always be revoked by the data subject.

Recruiting into research …

* It is still permissible under HIPAA to discuss recruitment into research with patients for whom such involvement might be appropriate. This common practice is considered to fall within the definition of treatment, at least when the conversation is undertaken by one of the patient's healthcare providers. If the contact will be made by someone other than the patient’s healthcare provider, permission will be required.

The HIPAA "minimum necessary" standard applies…

* Uses and disclosures of data for research that are allowed to bypass the authorization requirement are still subject to the "minimum necessary" standard - that is, the uses/disclosures must be no more than the minimum required for the described research purpose. A covered entity may rely on a researcher's documentation - or the assessment of an IRB or Privacy Board - that the information requested is the minimum necessary for the research purpose. By contrast, research information obtained using an authorization is not bound by the minimum necessary standard – on the theory that the data subject has given explicit permission in accordance with the signed authorization. However, be aware that while HIPAA may not require a minimum necessary justification at all times, an IRB's evaluation of risks and burdens on human subjects arguably does.

Under HIPAA, a “disclosure accounting” is required:

* In addition to being limited to external disclosures, disclosure accounting is not required for disclosures made under authority of a consent/authorization, on the theory that the data subjects are aware of what they have expressly permitted for that research. Neither is an accounting required for disclosures to the data subject directly about him/herself. Nor is it required for limited data set disclosures subject to a data use agreement. Nor, finally, is any accounting required for de-identified information that no longer qualifies as PHI.

If you're unsure about the particulars of HIPAA research requirements at your organization or have questions, you can usually consult with:

* If you are unsure about the particulars, consult with your organization's IRB, Privacy Board, or privacy official. For data security issues, consult with your organization's security official. Consulting with an experienced colleague can always be helpful, but their advice is not authoritative. Do not assume that a representative of the funder will know all the rules, or that the generic advice of a professional association will be applicable to your organization’s particular rules.

**Conflicts of Interest in Human Subjects Research**

The peer review process can create conflicts of interest because the choice of who reviews a potentially publishable project may show:

* Conflicts of interest may arise in the peer review process (for example, bias causes a reviewer to respond positively to a manuscript because it involves research or methodology in which the reviewer has a personal interest).

What is the term for management controls that are built in to a research study (for example, independent data analysis)?

* When developing conflict of interest management plans, COI committees typically examine the study design to determine whether it includes inherent controls that mitigate the researcher’s opportunity to bias the research. Inherent controls may include independent data analysis, randomization, blinding, or low subject enrollment percentage at a local site for a large multi-center trial.

An example of an institutional COI is:

* An institutional COI can arise when the financial interests of an organization or institutional official (acting within his or her authority on behalf of the organization) may affect or appear to affect the research conducted under the organization’s auspices. This could include significant gifts received by the organization from the sponsor of human subjects research.

The COI management plan aims to:

* A COI management plan is a document that explains the procedures or extra steps to be taken to minimize the risk of bias. The procedures or protections put into place to minimize the risk of bias are often called controls. Management plans are typically tailored to the study and the researcher’s financial interests. Management plans are not designed to eliminate COIs, nor reduce IRB regulatory review burden. Although management plans may be used for single site or multi-center research, their aim is to provide controls not just address disclosure of COIs.

The FDA regulations governing disclosure of individual COIs require:

* The FDA’s regulation governing disclosure of individual COIs requires applicants submitting marketing applications for drugs, biologics, or devices to certify the absence of certain financial interests or to disclose financial interests of researchers who conducted clinical studies covered by the regulation. The regulation specifies that the FDA may refuse to file any marketing application that does not contain a disclosure of researchers’ financial interests or a certification that the applicant acted with due diligence to obtain researchers’ disclosures, but was unable to do so.

An example of an individual financial COI is:

* An individual COI may arise when an individual has a personal or financial interest, which may affect or appear to affect the design, conduct, or reporting of the research.

The FDA regulations governing disclosure of individual COIs require:

* The FDA’s regulation governing disclosure of individual COIs requires applicants submitting marketing applications for drugs, biologics, or devices to certify the absence of certain financial interests or to disclose financial interests of researchers who conducted clinical studies covered by the regulation. The regulation specifies that the FDA may refuse to file any marketing application that does not contain a disclosure of researchers’ financial interests or a certification that the applicant acted with due diligence to obtain researchers’ disclosures, but was unable to do so

A researcher calls you stating that he plans to submit a proposal to the NIH for a human subjects research study. He wants to know at what point he and his study team must submit COI disclosures to comply with the PHS regulation.

* The NIH is a PHS agency. Therefore, this proposed research is subject to the PHS regulation regarding objectivity in research, which requires researchers to submit COI disclosures no later than the time a proposal is submitted to a PHS funding agency.

The PHS regulations about financial conflict of interests require which party to disclose significant financial conflicts of interest?

* The PHS regulations about financial conflict of interests require the researcher to disclose significant financial conflicts of interest to the organization. The FDA’s regulation governing disclosure of individual COI requires applicants submitting marketing applications for drugs, biologics, or devices to certify the absence of certain financial interests or disclose financial interests of researchers who conducted clinical studies covered by the regulation.

# Vulnerable subjects - Research Involving Workers/Employees

Vulnerable persons are those who are less able to protect themselves than other persons in a given situation. The Common Rule (45 CFR 46, Subpart A) has specific requirements for the following vulnerable populations, except:

* The Common Rule does not classify workers as a vulnerable population. The categories of vulnerable populations provided for in the Common Rule are children, prisoners, and individuals with impaired decision-making capacity.

When workers are asked to participate in a research study, vulnerabilities related to the subject's employment may include:

* Workers who serve as research subjects at their place of employment are vulnerable to numerous kinds of pressure from their co-workers, unions, and employers. Pressure can be applied to workers in subtle ways (such as, an employer who comments that if the research concludes that the organization is spending more on healthcare than other similar organizations, there may be lay-offs).

Researcher access to confidential records adds to the vulnerability of workers who participate in workplace studies. Inappropriate release of identifiable private information could adversely affect a worker's retention of a job, insurance, or other employment related benefits. To avoid or minimize these risks, the study design must include adequate safeguards to protect the confidentiality of the information collected. A plan for the proper management of study data and records should clearly define:

* Researchers must recognize that the primary harm in social and behavioral research is the breach of confidentiality. This risk of harm is especially significant when the data being collected involves an employee's experiences at their place of employment (for example, a situation where the employer has ongoing efforts to reduce healthcare costs by getting rid of employees who they believe will cause their healthcare insurance premiums to rise).

When a research project includes the collection of biological samples, all planned future uses of the samples, identifiers, and the data obtained from the samples, must be fully explained to the research subject.

* Genetic information has the potential to cause significant harm to research subjects if inappropriately disclosed, including harm to a subject's privacy, social standing, family obligations, employment/employability, or insurance/insurability.

**ELECTIVE MODULES (YOU MUST COMPLETE AT LEAST 1 OF THE ONES BELOW)**

# Avoiding Group Harms - U.S. Research Perspectives

The results from research have been known to produce harms to members of the sampled population who do not actually participate in the research study. An example of the type of research that could result in group harms by stigmatizing members of the group (even for individuals who do not participate in the research) is:

* A study of the types and prevalence of sexually transmitted infections (STIs) in small rural towns in a midwestern state.

Which of the following practices can be effective in minimizing group harms?

* Community consultation is used with the community of interest to make sure that potential harms are recognized and understood, and that the study is designed to provide benefits to the community. Collaborative IRB review with tribal IRB's will also maximize the likelihood that group harms are minimized. On-going consultation ensures that group leaders are provided with accurate information about the research as it progresses. By planning disclosure of the research, the researcher informs the community about how the research results will be disclosed early on in the process to reduce the possibility of harms to the group as the research is published or presented.

Which of the following studies has the LEAST potential to create group harm?

* A Phase 3 clinical trial of a new anticancer agent in middle-aged women diagnosed with breast cancer is unlikely to cause group harms. It is thus unlikely that such a study will be harmful to women with breast cancer or to women in general who do not participate in the study. The results from other hypothetical studies listed have the potential to be distressful, to stigmatize or in another way harm individual members of the Group who did not actively participate in the research.

# Avoiding Group Harms - International Research Perspectives

The results from research have been known to produce harms to members of the sampled population who do not actually participate in the research study. An example of the type of research that could result in group harms is:

* Results from such genetic studies that contradict long held beliefs and traditions about the origins of west coast American Indian populations may cause harms to the social structure and belief systems of the Native American population. Community consultation with tribal leaders and approval by tribal councils will help minimize the social harms such research might impose. Although women and children are vulnerable populations, the studies described are unlikely to produce stigmatization or other group harms.

Which of the following practices can be effective in minimizing group harms?

* Community consultation is used with the community of interest to make sure that potential harms are recognized and understood, and that the study is designed to provide benefits to the community. Collaborative IRB review with tribal IRB's will also maximize the likelihood that group harms are minimized. On-going consultation ensures that group leaders are provided with accurate information about the research as it progresses. By planning disclosure of the research, the researcher informs the community about how the research results will be disclosed early on in the process to reduce the possibility of harms to the group as the research is published or presented.

Which of the following studies has the LEAST potential to create group harm?

* A Phase 3 clinical trial of a new anticancer agent in middle-aged women diagnosed with breast cancer is unlikely to cause group harms. Although the patient population is women and women are specifically recognized as a vulnerable population, the subjects will likely come from all walks of life. It is thus unlikely that such a study will be harmful to women with breast cancer or to women in general who do not participate in the study. The results from other hypothetical studies listed have the potential to be distressful, to stigmatize or in another way harm individual members of the Group who did not actively participate in the research.