Illinois Criminal Justice Information Authority

Social and Behavioral Research Course

Developed by Lauren Weisner, M.A., in compliance with the National Institute of Health's Required Education in the Protection of Human Research Participants

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Section 1

History and Ethical Principles of Human Subjects Research

Adapted from: Gleicher, L .(2019). *Protecting participants of social science research.* Illinois Criminal Justice Information Authority.

Introduction

Research rooted in the scientific method helps inform stakeholders, policymakers, programs, and the community at large; it is the foundation on which to prove or disprove theory, understand issues, build knowledge, and advance society. In social science research, individuals may be asked to participate in studies as "human subjects" to help increase knowledge and understanding on various topics. Individuals may agree to participate in focus groups, interviews, surveys, or observations for research studies and program evaluations. While individual participation can provide numerous social and individual benefits and improve the application of programs and practices, researchers must take ethical considerations into account when developing and conducting a study involving human subjects.

In the United States, human subject research has become more strictly regulated through local, state, and federal laws; however, federal regulations only apply to those research studies that receive federal funding (Steneck, 2007). While regulatory requirements may vary by locale and funding sources, the primary responsibility for conducting ethical research lies with researchers and staff involved in carrying out their studies (Steneck, 2007).

Research norms vary from field to field, but there are several shared values that bind all researchers together, including: honesty, accuracy, efficiency, and objectivity (Steneck, 2007). Responsible research adheres to these values, in addition to professional codes, government regulations and guidelines, institutional policies and guidelines, and personal responsibility (Steneck, 2007).

History of National and International Research Abuses

Many current principles, practices, and codifications of ethical and legal human subject research stem from a series of unethical, abusive, and harmful research involving humans—sometimes participating in research involuntarily or without their consent (Resources for Research Ethics Education, 2016). A series of social and medical research abuses, most notably stemming from World War II, led to a system of both international and federal ethical protections to better shield individuals from potential harm (Trochim & Donnelly, 2007). These international and federal regulating bodies have developed—and continue to critically review and revise—regulations related to human subjects research.

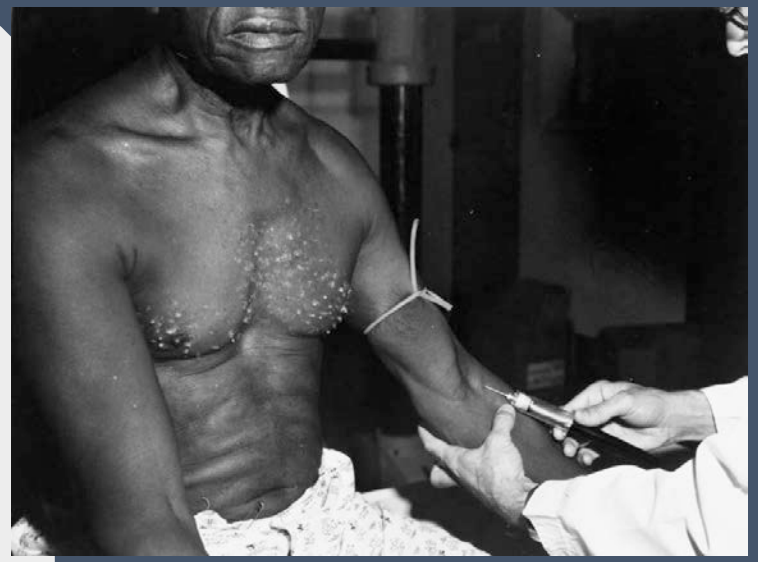
Two notable historical cases of research abuses that contributed to more critical examination of ethical standards for human subject research and deceitful research practices are The Nuremberg War Crime Trials and The Tuskegee Syphilis Study (Trochim & Donnelly, 2007).

Nuremberg War Crime Trials:

Held in the mid- to late-1940s, publicly exposed torturous and fatal involuntary human experiments conducted by Nazi physicians and scientists on prisoners in Nazi concentration camps (Shuster, 1997). This led to the development of the Nuremberg Code and the Declaration of Helsinki.

Tuskegee Syphilis Study:

Began in 1932 and spanned decades, was conducted by the Tuskegee Institute (now Tuskegee University) and the U.S. Public Health Service. The study experimented on Black men with and without syphilis in Macon County, AL, to document the natural progression of syphilis (National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, 2017). Study participants were not advised of their right to quit the study, informed of the study's real purpose, nor offered an effective treatment for the deadly illness, which was penicillin, available in 1947 (National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, 2017). This led to more explicit government regulation regarding the well-being of human subjects as part of research.



Historical cases indicate unethical practices also were performed during prestigious medical and behavioral studies on children with intellectual disabilities, cognitively impaired patients, and prisoners in correctional facilities (Cohen, 2017).

Responses to Historical Research Abuse

The Nuremberg Code

To address the use of inhumane research as documented in World War II, the Nuremberg Code explicitly detailed guidelines for the ethical treatment of human subjects in research. The Nuremberg Code consists of a set of directives for ethical human experimentation that focus on:

- Voluntary consent of the human subjects, with the liberty to disengage from research at any point of a study.
- Experimentation for societal good, that cannot be conducted by other means, and attempts to yield fruitful results.
- Research conducted, designed, and prepared in such a way to avoid all unnecessary physical or mental pain and suffering, injury, disability, or death.
- Studies conducted by scientifically qualified individuals.
- Researchers exercising good faith and superior skill and judgement, who are prepared to terminate experimentation if continuation is likely to result in injury, disability, and/or death.
- Research benefits that outweigh the risks (The Nuremberg Code, 1947).

Federal Regulations for Research Using Human Subjects

The Tuskegee Institute's syphilis study was stopped by an advisory panel created by the U.S. government in 1972 (National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, 2017). Soon thereafter, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created (herein referred to as the commission) in 1974 (Steneck, 2007). In addition, Congress required the then-Department of Health, Education, and Welfare (currently the U.S. Department of Health and Human Services) to create and clarify regulations regarding human subject research in the United States (Steneck, 2007)

The commission developed policies to protect human subjects of research studies, including a general policy for protection of human research subjects: Title 45 of the Code of Federal Regulations, Part 46 (45 CFR 46) (Steneck, 2007). In addition, the commission created additional guidelines through subparts B through D of 45 CFR 46 that protect vulnerable populations (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2013).

The commission also provided guidelines regarding reviews of research processes and protocols, disclosure of information, confidentiality and privacy, risks and benefits of research, institutional review board processes, and research compensation.

Belmont Report

Published by the commission in 1978, the Belmont Report summarizes the basic ethical principles to guide human subject research, outlining the principles that help inform moral judgements on fairness, appropriateness, and adequacy of the protections provided to human subjects as part of research (Steneck, 2007; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2013). The Belmont Report prescribed three basic principles to guide the decision-making process when conducting ethical human subject research: *respect for persons, beneficence,* and *justice* (Cohen, 2017). These principles are the accepted and common standard for decisions made by institutional review boards (IRBs), administrative bodies established to protect the rights and welfare of human research subjects recruited to participate in research activities (Steneck, 2007).

Respect for Persons:

Researchers should respect the autonomy of opinions and choices of people, refraining from potentially influencing a person's decision to participate in research, with additional protections for individuals with limited autonomy (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). This includes information on protocols of obtaining consent in addition to the voluntariness of that consent.

Beneficence:

Researchers should minimize the harm and maximize the benefits to those persons involved in research. This, however, does not mean that study participants are not exposed to potential risks, though potential risks must be justified based on the research's potential benefits to the individual, society, and/or knowledge (Cohen, 2017; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979)

Justice:

Researchers are obligated to select subjects equitably, and equally distribute the burdens and benefits of research (Cohen, 2017; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Thus, researchers cannot exploit specific groups of people due to those individuals' circumstances (e.g. poor, prisoners) (Cohen, 2017; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Researchers should critically evaluate whether subject selection is systematically selecting more vulnerable populations due to ease of access, ability to manipulate, or due to individuals' compromised position (e.g. prisoners) and not for reasons linked to the actual research study questions (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979)

Timeline of Human Subject Research Events

1932

Tuskegee Syphilis Study

The beginning of the unethical and deceitful study of syphilis progression of Black men in Alabama.

1945 -1946

Nuremberg Trials

Exposed torturous, involuntary human experiments on prisoners in Nazi concentration camps.

1947

Nuremberg Code

Ten directives created for ethical human experimentation.

1974

The National Research Act and 45 CFR 46

U.S. established the Commission to develop policies to protect human subject research. The Commission and Dept. of Health, Education, and Welfare (now Health and Human Services) created and clarified the "Common Rule" and its subparts for protection of vulnerable populations (45 CFR 46).

1979

Belmont Report

A summary of basic ethical principles of human subject research developed by the Commission, forming the basis of many federal regulation.

Current Federal Regulations

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research became inactive in 1978. Today, the U.S. Department of Health and Human Services' Office of Human Research Protections (OHRP) is the enforcing authority that oversees the protection of human subjects used in research conducted by federally funded agencies and individuals (Cohen, 2017; Steneck, 2007). Federal regulations are incorporated into the requirements of IRB applications and federally funded research. This includes 45 CFR 46 and its subparts, as well as the principles from the Belmont Report.

Subpart A of 45 CFR 46, referred to as the "Common Rule," sets out the basic requirements for privacy and confidentiality for human subjects involved in federally funded programs and research. Subpart A outlines the federal requirements related to IRB membership and operations; review research processes and approval criteria; documentation protocols; informed consent general requirements and protocols; and records in relation to the committee itself and requires assured compliance with federal regulations for IRB review and human subject research.

Subparts B through D provide additional protections for pregnant women, fetuses, and neonates involved in research; additional protections for biomedical and behavioral research involving prisoners as subjects; and additional protections for research involving children as subjects (Protection of Human Subjects, 46 C.F.R. § 46, 1991/2009; Steneck, 2007). In addition, 42 CFR Part 2 provides additional confidentiality and privacy protections around federally regulated or assisted programs that involve substance use disorder prevention, education, and treatment; these also include exceptions for research purposes.

To ensure federally funded research complies with federal regulations, individuals conducting such research are required training and certification in the protections of human subjects. However, the frequency with which this process should occur is not explicit within the regulations (Cohen, 2017; Collaborative Institutional Training Initiative (CITI) Program, n.d.; Office of Extramural Research, n.d.). The Collaborative Institutional Training Initiative (CITI), an online human subject research training collaborative, notes most organizations require refresher courses every three years (Collaborative Institutional Training Initiative (CITI) Program, n.d.). Any agency in which staff engages in human subject research also is required to file an “Assurance” of protection for human subjects with OHRP, formalizing their commitment to uphold these protections (Steneck, 2007).

Institutional Review Boards

Another mechanism of oversight for the protection of human subject research are institutional review boards (IRBs). IRBs are charged with overseeing the protection of the rights of human subjects in research (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). IRBs must review all federally funded human subject research protocols prior to the start of any research. However, research that is not funded by a federal agency does not require IRB approval of protocols and processes.

Federal regulations indicate IRBs can:

- Approve, disapprove, or modify research.
- Conduct continuing reviews of research.
- Observe and/or verify changes in research.
- Suspend or terminate approval for research.
- Observe the consent process and research procedures (Selqitz, Epley, & Erickson, 2018).

IRBs must adhere to federal requirements and are tasked with weighing the following for each study involving human subjects:

- Risks to subjects are minimized and whether risks identified are reasonable in relation to potential benefits and importance of knowledge gained.
- Equity of subject selection.
- Protocols for informed consent are appropriately documented and whether/how informed consent will be sought from the study subject participants.
- Protocols in the research plan provide adequate provision of monitoring data collection and use, ensuring the safety of subjects; and
- Protocols protect the privacy and confidentiality of research subjects are adequate (Steneck, 2007).

IRB member requirements include personally conducting or overseeing research; making sure all staff involved understand rules and regulations governing the research; ensuring fidelity to the research protocols outlined in the IRB-approved proposal; ensuring compliance with IRB requirements for reporting purposes, human subject confidentiality, privacy, and information security; obtaining informed consent; keeping thorough documentation of IRB protocols, processes, informed consent, and research activity; and ensuring any modifications or changes made to the research are first reviewed and approved by the IRB (Selwitz, Epley, & Erickson, 2018).

Researchers who do not follow IRB requirements and ethical guidelines may face the following consequences.

- Suspension of the research project and/or all of the principal investigator's research projects.
- Suspension and/or termination of all research at an organization.
- Inability to use or publish data and results from the research.
- Inability to receive federal grant funds.
- Increased and additional IRB monitoring and oversight and/or third-party oversight of research.
- Loss of license(s) and/or employment.
- Notification of non-compliance to sponsors, other regulatory agencies, and funding agencies (Selwitz, Epley, & Erickson, 2018).

Current Federal Regulations

Institutional Review Boards

IRB composition under the Common Rule is as follows:

- A minimum of five members who are diverse in gender, race, culture, and profession.
- At least one member whose main concern/profession is in a nonscientific area, as well as at least one member whose profession is in a scientific area.
- At least one member who is not affiliated with the organization housing the IRB.
- A member with experience/expertise in all areas of research that may come up for review, including vulnerable populations.
- Members with sensitivity to community attitudes.
- Members that understand organizational commitments and regulations, applicable laws, and standards of professional conduct and practice.
- Members who may have competence in special areas to help in research review that may be beyond IRB member capacity, per discretion of the IRB (Selwitz, Epley, & Erickson, 2018).

Freedom of Information Act

The Freedom of Information Act (FOIA) of 1966 allows for more transparency and public inspection of non-sensitive governmental information from federally funded research (see also *Forsham v. Harris (1980);* Monico, Bogucki, & Moore, 2013). However, FOIA also allows several exemptions, including protection of "personal privacy, trade secrets, national security, personnel records, and privileged communications" (National Research Council on Science, Technology, and Law Panel, 2002, p. 1).

The Shelby Amendment (part of FOIA) requires agencies to disclose data collected as part of federally funded research related only to published research findings from the study, or that data which "were used by the federal government in developing an agency action that has the force and effect of law," upon formal request (Auriti, Hamill, Kulkami, & Wu, 2013, p. 2). Exceptions are in place to protect confidentiality and privacy (National Research Council on Science, Technology, and Law Panel, 2002).

Further, only data related to federally supported, published research findings are required for disclosure under FOIA (Monico, Bogucki, & Moore, 2013). Researchers should remove personally identifiable information prior to disclosure, balancing privacy protections and intellectual property rights with research accountability and transparency (Fischer, 2013).

FOIA disclosure exemptions also include those listed in statutes compiled for law enforcement. They also may apply when release of records and other information could compromise adjudication or law enforcement processes, among others (Fischer, 2013).

The nine exemptions under FOIA are as follows:

1. Information classified to protect national security.
2. Information purely related to internal personnel rules and agency practices.
3. Information prohibited from disclosure by another federal law.
4. Confidential or privileged trade secrets, commercial, or financial information.
5. Communication between agencies that is privileged, including deliberative process privilege, attorney-work product privilege, and/or attorney-client privilege.
6. Information that would invade another's individual personal privacy if disclosed.
7. Information compiled for law enforcement purposes that could reasonably be expected to interfere with law enforcement proceedings and investigations; privacy, safety, and confidentiality of an individual; and/or impede the rights of an individual.
8. Information regarding supervision of financial institutions.
9. Geological information on wells

Additionally, Illinois maintains additional FOIA requirements that may affect research not explicitly protected from disclosure by Federal law. For the statute, please see: http://www.ilga.gov/legislation/ilcs/ilcs3.asp?ActID=85&ChapterID=2.

Additional U.S. Privacy Protections

Family Educational Rights and Privacy Act

The Family Educational Rights and Privacy Act **(**FERPA) protects the privacy of individuals' education records for schools receiving U.S. Department of Education funds (Family Educational Rights and Privacy Act (FERPA), 2018). The Act requires written permission for disclosure of students' educational records from a parent/guardian or eligible student, with certain exceptions (Family Educational Rights and Privacy Act (FERPA), 2018). These exceptions include (but are not limited to): disclosure to "school officials" with a "legitimate educational interest" to have the information (which must be disclosed in the school's annual notification of FERPA rights); disclosure to another school a student seeks or intends to enroll; for financial aid application purposes; and/or postsecondary education information disclosure in connection with a health or safety emergency (U.S. Department of Education, 2015).

Health Insurance Portability and Accountability Act Privacy Rule

The Health Insurance Portability and Accountability Act Privacy Rule (HIPAA) was created with the understanding that the privacy and confidentiality of personal health information must be protected, while simultaneously recognizing researchers have legitimate needs to use, access, and disclose individually identifiable personal health information to conduct vital, potentially life-saving research. This set of federal regulations provides information on when and which protected health information may be used or disclosed by "covered entities" for research purposes (Department of Health and Human Services, 2018). Covered entities include "health plans, health care clearinghouses, and health care providers who electronically transmit any health information in connection with transactions for which the Department of Health and Human Services has adopted standards" (Department of Health and Human Services, 2018). Some government agencies, such as health departments, may be considered covered entities or "hybrid entities," if the agency engages in both covered and non-covered functions (Department of Health and Human Services, 2018).

Covered entities may disclose personal health information in the following manner, per the HIPAA Privacy Rule:

1. Through written authorization for release of information from the potential human subjects (Office for Civil Rights, 2015).
2. Through use or disclosure of deidentified, protected health information for research purposes in accordance with 45 CFR 164.502(d) and 45 CFR 1.64.514(a)-(c) as defined by the HIPAA Privacy Rule.
3. Through securing a waiver of authorization provided and approved by an IRB or Privacy Board (45 CFR 164.512 (i)) (National Institutes of Health, 2004)

In addition, HIPAA allows a covered entity to use or disclose identifiable protected health information for research purposes without individuals' authorization if the covered entity obtains one of the following from the researcher:

- Documented approval from an IRB or Privacy Board.
- Written or oral description that the use or disclosure of protected health information is for the purposes of research protocol preparation or other preparatory research purposes (e.g. feasibility study).
- Written or oral description that the protected health information for use or disclosure is solely for research of decedents.
- A data use agreement between the researcher and covered entity for use of a limited data set in which specific identifiers are excluded and in compliance with several stipulations regarding use and transmission of the data (Office for Civil Rights, 2015*).*

Conclusion

Responsible research plays an important role in new information, growth, and improvement in the body of knowledge in social sciences. There can be many social and individual benefits from research study participation as a human subject. Most frequently, research provides a social benefit or outcome that is socially valuable (Resnik, 2008). For example, this may be increasing knowledge, informing new policies or programs that may benefit society or discovering new treatments. On an individual level, this benefit may be learning something new that may benefit you or receiving treatment that one may otherwise not receive in a clinical setting.

The unfortunate history of research abuses ultimately resulted in comprehensive principles, guidelines, and federal and state regulations to protect human subjects as part of research. This includes consequences for conducting unethical or harmful research, which can result in legal ramifications. Human subject research protections attempt to balance the necessary privacy, confidentiality, and welfare of a research subject, while recognizing the necessity and role that research has in conducting studies ethically and humanely to further knowledge.

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Section 2

Principal Investigator Responsibilities for Researchers

Adapted from: University of Wisconsin- Madison. (2019). *UW-Madison human subjects research infrastructure.*

Introduction

The purpose of this section is to provide a basic understanding of the responsibilities of the principal investigator involved in the conduct of human subjects research. By the end of this section, you will be able to describe the role of the principal investigator (PI) and the responsibilities that accompany that role.

Principal Investigator

The term principal investigator, also referred to as the PI, is used to identify a researcher with primary responsibility for a research project.

Responsibilities of the PI include (but are not limited to):

- Comply with the principles of the Belmont Report and adherence to the regulations outlined in the Common Rule and other applicable regulations.
- Provide adequate training to and oversight of study personnel.
- Obtain written documentation of IRB approval, or exemption, of the study prior to initiating human subjects research.
- Ensure that legally effective informed consent has been obtained, using an adequate and appropriate consent process, and ensuring the consent process is documented appropriately unless the IRB has granted a waiver of informed consent or documentation of informed consent.

- Ensure permission for the use and disclosure of protected health information is obtained in compliance with the HIPAA Privacy Rule if the research staff are within the Health Care Component or part of the Affiliated Covered Entity.
- Ensure compliance with the conditions of IRB approval, which includes following the procedures and using the materials within the IRB-approved application and protocol. In the case of exempt human subject research, monitor for changes that could alter the exemption determination and consulting with the IRB as necessary.
- Obtain IRB approval prior to the implementation of changes of protocol and promptly report changes of protocol.
- Submit continuing review progress reports in a timely manner.
- Report unanticipated problems to the IRB.
- Report noncompliance to the IRB.
- Ensure adequate records are kept to document study procedures and adherence with the IRB-approved application and protocol, as well as ensuring the records are retained and accessible for the required retention period
- Ensure that additional procedures are in place for investigator-initiated, multicenter studies.

COMPLIANCE WITH APPLICABLE REGULATIONS, LAWS, AND POLICIES GOVERNING HUMAN SUBJECTS RESEARCH

ICJIA maintains a Federalwide Assurance (FWA) with the U.S. Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP). The FWA states that all human subject research activities will be guided by the ethical principles outline in the Belmont Report and that federally supported research activities comply with the Common Rule. Investigators should become familiar with these principles and regulations to ensure that their research complies with them. Failure to comply with these principle can place both subjects and ICJIA at risk.

OVERSIGHT AND SUPERVISION

Although PIs may delegate certain research-related tasks to other members of the research team, they retain ultimate responsibility for the conduct of the study. The PI is the person ultimately responsible for the legal and ethical conduct of the study in accordance with the protocol, signed investigator agreements, and applicable regulations. The PI must be qualified by education, training, or experience to assume this responsibility.

Investigators are responsible for certifying that key personnel have received adequate training to ensure they are aware of the regulations governing human subjects research and understand and adhere to the IRB-approved research protocol. Compliance with these standards provides assurance that the rights, safety, and well-being of human subjects are protected and the integrity of the data collected.

Certain tasks may be delegated to qualified members of the research team, but the responsibility for ensuring tasks are performed in accordance with the protocol and regulations is the PI's, and cannot be delegated. The PI should ensure that a member of the research team to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task(s). PIs must also ensure that adequate resources are available for the conduct of the study. The investigator should have sufficient time and adequate resources to properly and safely conduct the research.

OBTAINING IRB APPROVAL OR EXEMPTION TO CONDUCT HUMAN SUBJECTS RESEARCH

Before initiating a study, a PI must obtain approval by the IRB to conduct human subjects research or a determination by the IRB that the study is exempt from IRB review. To be considered "human subjects research," a project must meet both the federal definitions of "research" and "human subjects".

Research is defined under the Common Rule as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

The Common Rule defines a "human subject" as a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

The Common Rule identifies eight categories of human subjects research that may be eligible for exemption from IRB review. Human subjects research that qualifies as exempt under one of the federal categories must nonetheless satisfy the ICJIA's ethical standards for the protection of human research participants. If an investigator thinks his or her research falls into one of these exemption categories, he or she must still submit a protocol to an IRB. Only an IRB can determine whether the human subjects research is exempt. The IRB has the right not to exempt a protocol and to require full review by the convened IRB or expedited review by an IRB member or IRB subcommittee, particularly if the research involves a sensitive population or sensitive topic. If a study is determined to be exempt from IRB review, it is not subject to continuing review or other rules governing human research, such as rules on informed consent. However, the HIPAA Privacy Rule applies to all exempt research that uses protected health information (PHI). HIPAA Privacy Rule requirements do not apply to exempt research using information that has been de-identified.

INFORMED CONSENT

Unless the IRB determines that a waiver of informed consent or waiver of a signed informed consent document is appropriate for a study or has determined a study to be exempt, an investigator is responsible for ensuring:

1. Informed consent is obtained and documented using only current IRB approved consent forms, and
2. The subject receives a copy of the informed consent document, and
3. Informed consent is obtained prior to the conduct of research procedures.

Consent documents with the IRB approval and expiration dates should be used to obtain written consent from subjects. All subjects must be given a copy of the consent form. PIs are responsible for ensuring the conduct of an adequate and appropriate consent process. When referring to "Informed Consent", it is important to differentiate between the informed consent document and the informed consent process.

Obtaining informed consent is a process and not solely obtaining a signature on a form. PIs are required to ensure that the consent process is conducted and is appropriate for the research study and subject population. PIs are responsible for ensuring the consent process is documented appropriately. Unless the IRB has granted a waiver of informed consent or a waiver of informed consent documentation, the study team should have a process in place to document the consent process, and any assent process (in the case where minors or individuals with impaired decision-making capacity are enrolled) in the research files for each subject

COMPLIANCE WITH THE IRB APPROVED PROTOCOL AND APPLICATION

Research teams must adhere to the conditions of IRB approval, which includes the information provided in the IRB application and any supporting materials such as a formal study protocol. This means the research team cannot perform any procedures, visits, or interactions that are not in the IRB-approved protocol and they must also perform what is specified in the protocol.

REQUIREMENTS AFTER IRB APPROVAL--CHANGES OF PROTOCOL

If modifications to the IRB approved materials are necessary, an amendment must be submitted to, and approved, by the IRB prior to implementing the change. Failure to conduct the study according to the IRB approved protocol is considered noncompliance. To change any aspect of a research study, including revisions to an approved protocol, consent documents, HIPAA authorization forms, instruments, and recruitment methods and materials, an amendment be submitted to the IRB for review and approval.

REQUIREMENTS AFTER IRB APPROVAL--CONTINUING REVIEW

Federal regulations require IRBs to review and approve research protocols at intervals appropriate to the degree of risk. As a courtesy, the IRB manager sends email reminder notices to study teams, including PIs, prior to the expiration of approval date. However, investigators are responsible for monitoring their approval periods and submitting a renewal form for IRB review in a timely manner. If IRB approval of a protocol expires, research activities must cease until re-approval of the protocol is obtained unless the PI demonstrates that procedures are necessary to ensure subject safety.

REQUIREMENTS AFTER IRB APPROVAL– UNANTICIPATED PROBLEMS

Federal regulations and institutional policies require that investigators report to the IRB any unanticipated problems that pose risks to subjects or others that are related to the research. These should be reported to the IRB in accordance with the campus unanticipated problems policy. Unanticipated problem is a broad term that includes not only unfavorable outcomes that have occurred that were not expected, but also the development of potentially increased risks of harm occurring in the future. According to guidance developed by the Office for Human Research Protections (OHRP), an unanticipated problem is an incidence, experience, or outcome that meets all 3 of the following criteria:

1. The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents.

2. The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
3. The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

REQUIREMENTS AFTER IRB APPROVAL: NONCOMPLIANCE

Federal regulations and institutional policies require that investigators report noncompliance with IRB-approved documents or research regulations to the IRB. Noncompliance means any failure to follow (1) federal regulations, state laws or institutional policies relevant to human subjects research, or (2) the requirements and determinations of the reviewing IRB.

RECORD KEEPING AND RECORD RETENTION

State and federal regulations require study teams to maintain complete and accurate study records. Study records should be stored in a secure manner to protect the privacy of subjects and to reduce the risk of damage. Any or all of the study related documents may be subject to, and should be available for, audit or inspection by a regulatory authority. Study records can be archived after completion, but must be maintained for a specified amount of time, depending on the requirements of the funding agency, sponsor, FDA or entity providing oversight. There may be other requirements that researchers must look into before disposing of research records; for example, the institution recommends maintaining records for at least three years to dispute any allegations of research misconduct.

ADDITIONAL RESPONSIBILITIES FOR MULTI-SITE RESEARCH

When IRB review of a study is deferred to a non- ICJIA IRB, the PI and study team must still comply with relevant ICJIA requirements and must also be familiar with the requirements of the IRB of record, which may differ from that required by ICJIA. These responsibilities include complying with the requirements of the reviewing IRB in addition to those of the PI's own institution and ensuring all institutional requirements are met in addition to the PI's own institution. Research approved by another IRB may still be subject to ICJIA IRB review at the Executive Director's discretion.

When ICJIA serves as the coordinating center for a study, some of the additional requirements the PI and study team are responsible for include ensuring IRB approvals from all sites are in place before human subjects research occurs at those sites and promptly communicating changes of protocol, new information, and unanticipated problems to all study sites and ensuring that any changes are implemented.

Section 3

Defining Research with Human Subjects

Adapted from: Hicks, L.(n.d.). *Defining research with human subjects.* Collaborative Institutional Training Initiative.

Introduction

If a project involves human subjects research, an institutional review board (IRB) must review. The federal regulations define “research” and “human subjects” at 45 CFR 46.102.

Defining Research

Under 45 CFR 46, research is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge"

The following activities are not deemed to be research:

1. Scholarly and journalistic activities (*e.g.,* oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Defining “Systematic Investigation”

The definition of research starts by stating that the activity must be a systematic investigation. A systematic investigation is the opposite of a disorganized, random venture. In other words, researchers need to have constructed a research plan with ideas about what they want to learn and how best to do that.

Both qualitative and quantitative researchers use systematic investigation in the course of their research. Both types of research are organized, albeit around differing notions about the role of the researcher, the purpose of the research, the nature of the data collected, and so on.

Quantitative researchers may test hypotheses and theories with the data they collect, while qualitative researchers may generate hypotheses or theories based on the data they gather. Quantitative researchers may focus on statistical analyses based on precise measurements; however, it is not necessary for precise, replicable measurements to be collected in order for research to be considered systematic.

“Research Development, Testing and Evaluation”

It is important to understand what activities qualify as “research development, testing, and evaluation” under the definition of research.

Pilot studies and other preliminary studies fall under the definition of research. Both of the following preliminary components of a study constitute research with human subjects:

- Convening a focus group to help researchers develop a questionnaire
- Pilot testing a questionnaire

“Designed to Develop or Contribute to Generalizable Knowledge”

The definition of research requires that the activity is designed to develop or contribute to generalizable knowledge. Generally speaking, “to generalize” means to draw broad, general conclusions by inferring from specific cases. Although some qualitative research may be less generalizable than some quantitative research, it is not the case that only hypothesis-driven, replicable research may be considered generalizable. Even research about the most narrowly defined topic (such as, an individual case study or an isolated community study) may be intended to contribute to a body of knowledge (such as, the function of culture, expression of gender, or political views of marginalized community members).

There is no regulatory guidance on the meaning of generalizability. The essential consideration is whether it was the researcher's intent to contribute to a body of knowledge or whether the results were replicable. **It really depends on the intent**.

Some activities that involve interactions with humans and data gathering may not meet the definition of research because they are designed to accomplish something else, such as program improvement (also called quality improvement activities).

For example, university library staff may conduct a survey of members of an academic unit to find out if the library is meeting the department's need. The project may be a systematic investigation, but is not considered research because the intent of the project is to improve the library's service to its patrons, rather than contribute to a body of knowledge (such as, improving all libraries' service methods).

Publication of results is sometimes used, incorrectly, as an indicator that a project meets the definition of research. It is the intent of the project that matters. In the example above, the library staff could share the results of their program improvement activity at a conference without changing the intent. The project would not become research by virtue of sharing its results.

Defining Human Subjects

The federal regulations define human subjects as “a living individual about whom an investigator 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”

“A Living Individual”

Under the federal regulations, research involving deceased individuals does not meet the definition of research with human subjects.

“About Whom”

Some research that involves interactions with living individuals does not meet the regulatory definition of research with human subjects because the focus of the investigation is not on the opinions, characteristics, or behavior of the individual. Instead, the individual is asked to provide information about something. How many micro-loans were made last year? What is the average amount of those loans? These are not "about whom" questions, but can be thought of as "about what" questions.

If a researcher calls the director of a shelter for battered women and asks her for the average length of stay of the women who use the shelter, that inquiry would not meet the definition of research with human subjects, even though there is an interaction between the researcher and a living individual, because the information requested is not "about" the director. If the researcher interviewed the director about her training, experience, how she defines the problem of battering, or how she manages stress, then the inquiry becomes about her - and thus "about whom" - and therefore, meets the definition of research with human subjects.

“Through Intervention or Interaction”

The researcher must obtain the information or biospecimens about the subjects either by intervention or interaction.

Interactions can include:

- Communication or interpersonal contact between the subject and the researcher such as online surveys that do not ask for any identifiable information
- Participant observation, often including both formal and informal interviews in addition to observation

Interventions can include:

- Behavioral interventions such as experimental education programs or unproven psychosocial therapies
- Manipulation of the subject or the subject's environment performed for research purposes

“Private Information” and “Identifiable Private Information”

As defined in the Common Rule, **private information** “includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.,* a medical record).

Identifiable private information is defined as “private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information”

The regulation further requires that federal agencies implementing the Common Rule must reexamine the meaning of “identifiable private information” regularly, especially in light of emerging technologies and techniques that can be used for identification/re- identification purposes.

Observing and Recording Private Behavior

It is important to keep in mind that whether a setting is public, by federal definition, is determined in large part by the potential subjects' reasonable expectations of privacy, rather than any absolute distinctions between public and private spaces.

For example, one might expect that certain behavior, even if conducted in public spaces, is in fact private, such as a conversation in a public park. It is reasonable to assume that one might expect not to be taped while dining with a date at a restaurant.

Researchers who wish to obtain information in a context in which subjects would have a reasonable expectation of privacy, may choose to use covert observation (concealed audio or video recording devices, or using a one-way mirror) or assume a role in the setting or group being studied. Such studies raise significant concerns about violation of privacy and require additional protections and safeguards for subjects. Observational studies in quasi-public places, for example, hospital emergency rooms, also may raise such concerns.

Private Information Provided by Individuals for Specific Purposes

Individuals, in a variety of settings, provide personal information with the expectation that it not be made public, such as at work, at school, when receiving health care, or as a member of an organization. Some of this personal information is protected by law. Additional laws to protect individuals' privacy include:

- The Family Education Rights and Privacy Act (FERPA) protects the privacy of school records. Similarly, the privacy provisions of the Health Insurance Portability and Accountability Act (HIPAA) protect private health information. Generally, although there are some exceptions, school and medical records can only be released with express written permission.
- Data files including identifiable private information are compiled and maintained by both public and private institutions. Owners of identifiable data impose restrictions on the use of the data they provide researchers. Institutions may release de-identified data publicly, but only release identifiable data to researchers with IRB-approved data protection plans.

Section 4
Assessing Risk

Adapted from: Arwood, T. & Panicker, S. (n.d.). *Assessing risk.* Collaborative Institutional Training Initiative.

Introduction

One of the most important and challenging tasks researchers and IRBs face is identifying and evaluating risks of harm associated with participation in research. Unlike biomedical research studies and clinical trials in which the sources of risk may be more readily identifiable and quantifiable, potential harms associated with taking part in social and behavioral science research may be more ambiguous and less predictable, such as individual reactions to certain events or questions. However, identifying and assessing risks in such situations should be informed by a growing body of research literature on risks associated with research participation.

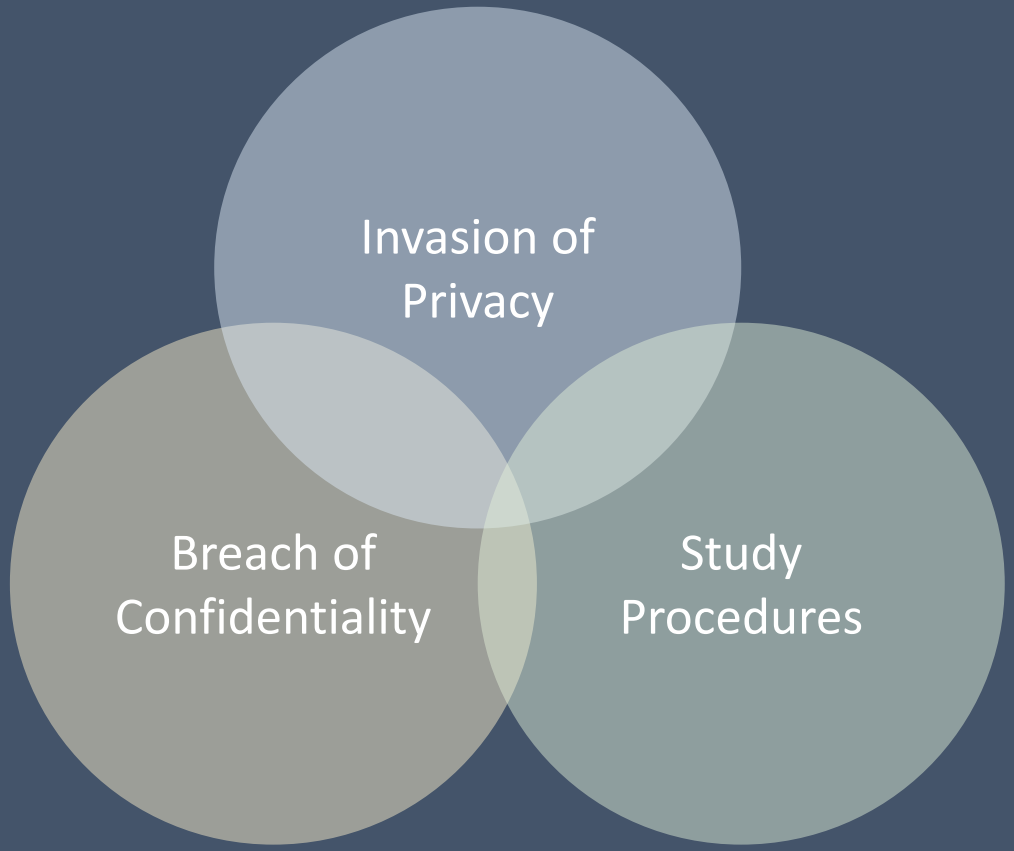
The risks of harm typically associated with social and behavioral research are social, psychological, economic, and legal in nature. However, in rare circumstances, the risks may involve physical harm. For example, those who study victims of domestic violence need to consider that individuals taking part in the study may become the victims of retaliatory violence if the subjects' involvement in the research is discovered.

It also is possible that when groups or communities rather than individuals are the focus of a study, the group as a whole may be at risk of harm. For example, research on the prevalence of individuals with HIV in communities may stigmatize the community being studied.

Identification, assessment, and minimization of risk are paramount to the conduct of ethical social and behavioral research.

Identifying Risks Associated with Research Participation

Risks of harm in social sciences typically fall into three categories:



Invasion of Privacy

Invasion of privacy can occur if personal information is accessed or collected without the subjects' knowledge or consent. For example, if a researcher studying interaction patterns in an online support group joins the group and does not reveal her true identity online, the support group participants could feel that their privacy had been invaded by the researcher, if or when her true identity as a researcher is revealed to the group.

Invasion of privacy also can occur if a subject's participation in a study is revealed despite assurances that this would not happen. For example, a researcher is studying emotional reactivity in women who have experienced sexual abuse. The research is conducted in a designated university lab on a particular day each week. Another university staff person sees an acquaintance entering the meeting room and therefore discovers that the acquaintance has experienced sexual abuse.

Breach of Confidentiality

Perhaps the primary source of potential harm in the social and behavioral sciences is that information obtained by researchers could adversely affect subjects if disclosed outside the research setting. Confidentiality can be compromised through an unauthorized release of data, which could have a negative impact on the subjects' psychological, social, or economic status. For example:

- Disclosure of worker attitudes toward manager effectiveness could result in job loss if the information is not protected
- Information about illegal activities or immigrant status can have serious legal consequences for subjects
- Public revelations about sexual orientation could result in psychological stress

Study Procedures

In some cases, simply taking part in research can put subjects at risk. For example, if a researcher is conducting interviews with individual gang members, it may be necessary to find places to meet where other gang members could not observe the interaction.

Another situation in which merely taking part in research might pose some risk to subjects is when there is a potential for a breach of confidentiality, not because of inadequate confidentiality procedures on the part of the research team, but from subjects themselves when data are collected in a group setting such as a focus group. Even though participants typically are cautioned not to share information outside the data collection setting, subjects should be made aware that the researcher cannot guarantee confidentiality.

Often it is assumed that the very nature of the research inquiry can pose risk of harm to subjects. For instance, when reviewing research plans that involve asking subjects questions about trauma or abuse, IRB members may be concerned about retraumatization. However, current research findings indicate that when appropriate protections are built into the study design, such as ensuring that interviewers are trained to ask questions in a supportive, respectful manner and respond to subjects' reactions appropriately, very few subjects were upset.

In fact, most subjects, including those who may have experienced fleeting negative emotions, reported feeling good about taking part in the study (Cromer & Newman 2011). Thus, it is important to review the literature in a given field to determine what, if any, risk of harm the research topic or design might pose to the participant and what additional protections may be necessary.

Assessing Risk

When assessing risks of harm associated with participation in a research study, there are two distinct elements of risk that must be considered. One is the probability of harm - the likelihood that a specific harm might occur. The fact that not all possible harms are equally probable should be taken into consideration when assessing risk. The second element of risk is the magnitude or severity of harm should it occur. The interaction between these two elements is a crucial factor in determining the level of risk of harm in a study.

Often there is disparity between the probability and the magnitude of risk of harm in a study. For example, a researcher wants to do a web-based survey of college students to collect information about their sexual behavior and drug use. Direct identifiers will not be collected; however, Internet Protocol (IP) addresses may be present in the data set. Although the probability that an individual subject could be identified is low, the magnitude of the possible risk of harm is high given the sensitivity of the information.

Situation and Time

Risks of harm in research participation are specific to time, situation, and culture. What may be a socially sensitive issue or topic at one time or place may not be so at another time or place. For example, asking women if they have had an abortion would carry very different risks in a country where abortion is a routine medical practice, a country where it is illegal, or a country in which it is legal but the issue is fraught with religious and political controversy.

Subject Population

Risks of harm will differ according to the subject population, too. Consider this case: A study on the efficacy of a behavioral intervention for smoking cessation involves both adults and teenagers. Purchasing tobacco products is generally illegal for persons under 18 years of age. For adults, however, it is a health hazard, but not an illegal activity. Thus, any assessment of the risk for teenagers will have to consider that the research focuses on an illegal activity. Similarly, a survey about sexually transmitted diseases may carry different risks for different subject populations.

Assessing Risk Objectively

It may be challenging for researchers or potential subjects to assess risk objectively. Researchers may underestimate the risks involved in activities with which they are familiar and overestimate the benefit of things that are important to them.

Regardless of the true probability of harm, research indicates that when potential harms are severe, people tend to overestimate the probability. When potential harms are less severe, such as embarrassment, people tend to underestimate the probability. An independent assessment of risk is critical. One function of IRBs is to provide this independent assessment

Balancing Risks and Potential Benefits

Federal regulations, based on the ethical principle of beneficence, require that risks of harm associated with research are reasonable in relation to the potential benefits.

A great deal of research in the social and behavioral sciences offers little potential for direct benefits to the subjects themselves. The benefits of the research often lie in the importance of the knowledge to be gained, the contributions it makes to science, or the contributions to society in general. There also might be cases in which a specific community, rather than individual subjects, benefits from the research. This should be balanced with the fact that most research in the social and behavioral sciences poses little or no risk of harm to the individual subject.

In addition, regulations stipulate that risks of harm must be minimized to the extent possible, consistent with sound research design.

In order to minimize risk, potential research subjects need to be given sufficient information to make a decision about whether they are willing to accept risks and participate in the research. If research questions will be of a sensitive nature, subjects need to be forewarned. Subjects also need to know what steps will be taken to protect confidential information, including disposition of recorded material. Any limits to the extent to which a researcher can protect identifiable personal information should be clearly explained. State and local laws may limit confidentiality, such as reporting requirements for child and elder abuse. Confidentiality cannot be guaranteed for information shared in a focus group.

Minimizing and Managing Risk

It is important to minimize and manage the risks of harm in the research study. Researchers and IRBs should assess the potential risks of harm in the study to determine the best minimization and management plan.

When the Primary Source of Risk is the Data

When a possible disclosure of subject responses is the primary source of potential harm, collecting data anonymously may provide the best protection. For example, a mailed survey can be constructed without a follow up procedure, thereby negating the need for identifiers.

If, however, the study design makes the collection of identifiers necessary, for example a longitudinal study, safeguarding the data from unauthorized access can be accomplished in various ways, including:

- Use of as few direct identifiers as practical.
- Remove all direct identifiers as soon as possible.
- Substitute codes for identifiers.
- Maintain code lists and data les in separate secure locations.
- Use accepted methods to protect against indirect identification, such as aggregate reporting or pseudonyms. Use and protect computer passwords.
- Encrypt transmitted and stored data.
- Access and store data on computers without internet connections.
- Minimize procedures involving transferring direct identifiers between persons.
- Obtain a Certificate of Confidentiality.

In the past, when data were usually recorded and stored on paper and/or devices such as floppy disks, researchers restricted access to data by storing the records in locked file cabinets, in locked file cabinets. With increasing use of digital technologies to acquire, transmit, analyze, and store data, data security has become much more complex. Researchers are not often information technology (IT) experts. Therefore, research teams should consult with their institutional IT security contacts for guidance regarding the most secure means of obtaining, transferring, analyzing, and storing data when the primary source of risk stems from a security breach.

Certificates of Confidentiality

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from compelled disclosure. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

A Certificate of Confidentiality will allow the researcher, and others who have access to research records, to be protected from required disclosure of identifying information on research participants in: civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level

The kinds of information that can be protected include:

- Substance abuse or other illegal behaviors
- Sexual attitudes, preferences, or practices
- Genetic information
- Psychological health

Certificates of Confidentiality do not override the requirement to report the suspicion of child abuse or neglect, or any other state-mandated reporting requirements, such as elder abuse. Other federal agencies, such as the Department of Justice, provide agency-specific protections that apply to research conducted or funded by the agency.

Under a policy issued 7 September 2017 (effective 1 October 2017), NIH-funded investigators do not need to apply for a Certificate of Confidentiality , nor will they receive a document certificate. The NIH issues Certificates of Confidentiality automatically for “NIH funded grants, cooperative agreements, contracts and intramural research projects research funded wholly or in part by the NIH that collects or uses identifiable, sensitive information” (NIH 2017). Certificates of Confidentiality contain conditions for disclosure of the identifiable, sensitive information that the investigator must comply with, including more restrictive requirements for disclosure in the new policy.

Privacy Certificates

For research funded through DOJ entities (e.g., BJA, BJS, NIJ, OVC) researchers can submit a privacy certificate. Unlike certificates of confidentiality, privacy certificates prevent researchers from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self or others– thus, if researchers expect to disclose this kind of information, they must include consent to report in consent forms.

Beginning with Fiscal Year 2017 funds, any JAG funded research must obtain a privacy certificate for the project.

Consent Forms and Certificates

Consent forms should reference the PC or the CoC. ICJIA's current consent template includes NIH recommended language that can be used to inform participants of the certificate and what it protects against. Make sure that the language included in the consent form references the correct certificate. Furthermore, do not include the language if you are not obtaining a privacy certificate.

When the Primary Source of Risk Is the Consent Document

Subjects may be placed at risk if others know they are taking part in a study of a stigmatizing or illegal activity. If the consent form is the only document that links the participants to the study, one way to diminish their risk of exposure is to consider applying to the IRB for a waiver of the requirement to document consent. A waiver of documentation of consent does not imply that any of the required elements of consent are waived. The elements of consent must be provided in some fashion such as in a cover letter, informational sheet, or verbal script.

Summary

Common social and behavioral sciences methodologies such as surveys, questionnaires, and interviews are considered (sometimes erroneously) low risk, because they do not involve physically invasive procedures with associated risk of physical harm. However, it is not the procedures per se that engender potential risks of harm, but the interaction of different factors. It is necessary to assess both the probability and magnitude of harm, as well as the context (situation, place, and time) of the research as it relates to the particular study population.

References

Cromer, L. D. & Newman. E. (2011). Research ethics in victimization studies: Widening the lens. *Violence Against Women, 17*(12), 1536-1548.

Section 5
Informed Consent

Adapted from: Hicks, L. (n.d.). *Informed consent.* Collaborative Institutional Training Initiative.

Introduction

There is general consensus on the importance of informed consent in research. Most people have the expectation that they will be treated with respect and as autonomous individuals. They also expect that they have the right to make decisions about what will and will not be done to them and about what personal information they will share with others.

However, researchers also are aware that there are circumstances in which obtaining and documenting consent in social and behavioral research may be a complex, and often challenging, process. For instance, potential subjects may be fluent in a language but not literate. Researchers may need to deceive research subjects in order to obtain scientifically valid data. Asking subjects to sign consent forms linking them to a study about illegal activities could put them at risk of harm.

The federal regulations (at 45 CFR 46, Subpart A) provide sufficient flexibility to address some of these concerns, particularly for research posing no more than minimal risk of harm. For example, the regulations allow waivers of and alterations in the requirements for the consent and documentation processes.

Key Terms

Broad Consent is prospective consent for unspecified future research using Informed Consent - identifiable private information or identifiable biospecimens.

Key Information is the concise and focused information presented at the beginning of a consent discussion that is most likely to assist an individual in understanding the reasons why or why not to participate in the study.

Legally Authorized Representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Vulnerable means subjects in research studies susceptible to the possibility of coercion or undue influence.

Overview of Informed Consent

Federal regulations require researchers to obtain legally effective informed consent from the subject or the subject's LAR. There are two parts to informed consent.

1. Provide information to prospective subjects
2. Document that the process took place and record the subject’s agreement to participate

Consent should begin with a concise and focused presentation of the key information that is most likely to assist a subject in understanding the research, what is expected of them, and the potential risks of harm and benefits.

Regulations require that this information be understandable to the subject and presented in a way that facilitates comprehension. The emphasis is on presenting information that a “reasonable person” would want to have in order to make an informed decision to participate, providing an opportunity to discuss, and ensuring subject (or LAR) comprehension.

In practice, informed consent forms often are used as a means to provide information about a study, and, when signed, serve as documentation of consent.

However, in some cases, an oral consent process without documentation may be approved by an Institutional Review Board (IRB). The regulation does allow the exchange of consent information to take place face-to-face or by mail, telephone, internet (online), fax, or video. An electronic format for the consent and signatures is also allowed.

The Process

Informed consent is a process that begins with the recruitment and screening of a subject and continues throughout the subject's involvement in the research. It includes:

- Providing specific information about the study to subjects in a way that is understandable to them.
- Answering questions to ensure that subjects understand the research and their role in it.
- Giving subjects sufficient time to consider their decisions.
- Obtaining the voluntary agreement of subjects to take part in the study. The agreement is only to enter the study, as subjects may at any time withdraw, decline to answer specific questions, or complete specific tasks during the research.

Documentation

Documentation of consent provides a record that the consent process took place. It generally consists of a consent form signed by the subject or the subject's LAR. In practice, this document often is used as a tool for engaging in the consent process. Informed consent may be documented by other means, such as audio or video recording, as approved by an IRB.

Required Information Provided to Subjects

Federal regulations at 45 CFR 46 list specific elements of information that must be provided to subjects about informed consent. The elements are divided into two categories. The first includes **basic elements** to be provided to subjects. The second lists elements that must be included if appropriate.

Basic Elements

The basic elements of informed consent list nine items that must be included, as noted in the regulations at 46.116(b). When appropriate, an analysis or commentary regarding the regulatory element is included in ***bold italics***.

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research. [***If there are no direct benefits, the researchers may tell subjects what they hope to learn, how that knowledge will contribute to the field of study or how the knowledge might benefit others if such a case can be made***.]
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. [***This requirement is primarily relevant for biomedical research. However, it might be applicable to social and behavioral research if behavioral interventions, such as novel teaching or therapeutic methods, are proposed.***]

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. [***The description must include a full disclosure of any state-mandated reporting requirements, such as suspicion of child abuse and/or neglect or harm to others. State requirements vary, so IRBs and researchers must be aware of state-specific information.***]
6. For research involving more than minimal risk, an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, what compensation will be provided, and where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research related injury to the subject. [***In some field research, there may not be any way for subjects to call or email anyone about their questions and concerns. Alternative means of communication must be established, such as a local contact on the research team.***]

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. [***Most researchers in the social and behavioral sciences are not in a position to impose penalties. However, specific study-related assurances that there will be no negative consequences associated with choosing not to take part might be appropriate. For example, parents may need to be assured that if they choose not to participate in a school-based, school-approved study their children's grades or placement will not be affected***.]
9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

i. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

ii. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies. [***The requirement does not apply to all research; only research that involves the collection of identifiable information or biospecimens. Research not involving the collection of information or biospecimens would not require this statement.***]

Additional Elements

Depending upon the nature of the research and the risks involved, there may be additional required elements, as noted in the regulations at 46.116(c). These additional elements are only required when applicable, so not all consent forms or discussions would include them. When appropriate, an analysis or commentary regarding the regulatory element is included in ***bold italics***.

1. A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. [***Subjects need to know, for example, how their compensation will be affected if they choose not to complete an interview. Discussion of what happens to data already collected if they withdraw midway through the study also may be addressed in this section.***]

5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject. [***This requirement applies primarily to biomedical research involving new treatments and procedures, but also may apply to research on experimental behavioral interventions.***]
6. The approximate number of subjects involved in the study.
7. A statement that the subject’s biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Incentives

Incentives are payments or gifts offered to subjects as reimbursement for their participation. These must be described during the consent process as well as the conditions under which subjects will receive partial or no payment. They must not constitute undue influence.

Both financial and non-financial incentives can potentially create undue influence. IRBs should ensure that incentives are not so great as to diminish the voluntariness of consent or cloud someone's appreciation of risks or potential benefits that might be gained from participating in a study.

Recruitment

Recruitment is part of the consent process because it begins the process of providing information about the study. All recruitment strategies such as fliers, email messages, newspaper advertisements, phone scripts, and so on must be reviewed and approved by an IRB before they are used.

Exculpatory Language

Subjects may not be asked to waive or even appear to waive any of their legal rights. They may not be asked to release a researcher, sponsor, or institution from liability for negligence. Institutions may provide information about how liabilities will be covered.

NON-EXCULPATORY LANGUAGE:
"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 the researcher or your right to other services that you may be eligible for."

EXCULPATORY LANGUAGE:
"You waive your right to sue or for compensation for injuries that you may receive as a result of participating in this study."

Broad Consent

Broad consent, as noted in the regulations at 46.116(d), is an optional alternative process of obtaining consent for the storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens. Researchers should consult with their institution and IRB policies as broad consent may not be implemented at all places

Ensuring Comprehension of Consent Information

Researchers are required to provide information in a manner understandable to the subjects. The regulations emphasize that consent must begin with a “concise and focused presentation” to the subject and provide information that would help the subject determine whether to participate.

Effective informed consent includes providing sufficient detail about the research and presenting information in a way that is not just a list of facts. This requires preparing material in the subject's language at the appropriate reading level. When a study is complex and/or the reading or educational level of the prospective study population is low, the role of dialogue and explanation becomes an even more crucial part of the consent process.

Ensuring Free Choice

The principle of respect for persons requires that participation in research be truly voluntary and free from coercion or undue influence. Even when a study is innocuous, subjects must be informed that they do not have to take part, and they may choose to stop participating at any time.

Setting and Time

Researchers should consider ways in which the setting of the consent process might include elements of undue influence. Potential subjects might not feel entirely free to choose whether to take part in a research study if they are:

- Adolescents whose parents are in the room
- Adolescents in a group of other adolescents being recruited for the same study
- Parents who receive a letter from the school principal asking them for permission to enroll their children in a study
- Athletes recruited by their coach Employees asked to take part by their employer

Safeguards for Vulnerable Subjects During Consent

Federal regulations state that IRBs must ensure that appropriate safeguards are in place to protect the rights and welfare of subjects likely to be vulnerable to coercion or undue influence. Potentially vulnerable subjects include children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. Additional safeguards for three groups are provided in the regulations:

- Subpart B for pregnant women, human fetuses, and neonates involved in research
- Subpart C for research involving prisoners as subjects
- Subpart D for children involved as subjects in research

Safeguards employed for vulnerable subjects include, among many other strategies, assessing the decision-making capacity of potential subjects, requiring parental permission from both parents rather than just one parent for some studies with children, and ensuring that incentives are not coercive

Informed Consent in Exempt Research

If an institution determines that a study meets the criteria for exempt research, the detailed regulatory requirements for informed consent in 45 CFR 46.116 do not apply.

However, research that is exempt from federal regulations is still research with human subjects and the ethical principles as outlined in the Belmont Report still apply. Each institution or IRB decides how to handle informed consent in research that is eligible for exemption from the regulations.

Under the 2018 Requirements version of the Common Rule, some exempt research requires a limited IRB review (administrative review). In two of the exempt categories, limited IRB review is required to ensure there are adequate confidentiality and privacy safeguards. In the other two categories, limited IRB review is required for broad consent in studies involving identifiable private information or identifiable biospecimens.

Remember, if an individual was asked to provide broad consent and refused, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

Waivers of the Elements of Consent

The federal regulations at 46.116(f) allow IRBs to authorize researchers to modify the consent process by omitting one or more elements of information or to provide no information at all. The waiver or alteration of any or all of the elements of consent can be authorized only if these five criteria are met.

1. The research involves no more than minimal risk to the subjects.
    a. Minimal risk means "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the daily life or during the performance of routine physical or psychological examinations or tests"
2. The research could not practicably be carried out without the requested waiver or alteration
    a. **Impracticable does not mean time consuming, expensive, or inconvenient.** It means that securing consent is not feasible, regardless of cost and time. Impracticable may mean that without a waiver it would not be possible to answer the research question. Disclosing the purpose of the research may influence how subjects respond.

3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.
    a. Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. In the absence of specific legal rights, this criterion is often difficult to apply because the federal regulations do not dene "rights and welfare." Also, the parties involved in the research process (researchers, IRBs, and the community of subjects) may not always agree on how to dene subjects' rights and welfare. When a waiver is required because the research involves deception, this requirement usually is interpreted to mean that subjects are not "tricked" into participating in a study that they would fi objectionable.
5. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.
    a. This process often is referred to as debriefing. The debriefing process is an opportunity to provide subjects with information not disclosed during the initial consent process. It also provides an opportunity for subjects to withdraw and not have their identifiable data participation. withdraw and not have their identifiable data included in the research. Note: Debriefing is not required in situations in which debriefing would cause more harm than good, for example, if subject selection was based on an undesirable or unflattering characteristic.

Waiver for Screening, Recruiting, or Determining Eligibility

Under 46.117(g), the IRB may also approve a research study when the investigator will obtain information or biospecimens for purposes of screening, recruiting, or determining eligibility for the study without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

1. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative.
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Examples of When Partial and Complete Waivers Would Be Used in Deception and Complete Non-Disclosure

In social and behavioral research, deception and complete non-disclosure of information to subjects may be necessary to avoid subject response bias in the research. The IRB must review the research plan for deception or complete nondisclosure of information to ensure there is adequate justification for the technique as well as an adequate debriefing plan for after the research.

Deception

Outright deception can sometimes be justified as essential for investigating a particular phenomenon. For example, subjects may be told that a study is about perception of visual phenomenon, when in fact it is about susceptibility to peer pressure from the researcher's confederates.

Complete Non-Disclosure

If people know that they are being observed, they may alter their behavior in such a way that obtaining meaningful results is not possible. Covert observation requires a waiver of all of the elements of consent if the research takes place in a setting in which subjects could reasonably expect that their behavior was not being observed and recorded.

Waivers of Parental Permission and Child Assent

An IRB may waive the requirement to secure parental permission for children to take part in research, in accordance with the same criteria for waiving consent.

The regulations do not include a list of elements that must be included in a child assent process. It is up to an IRB to determine whether child assent is required, what elements must be included in the assent process, and whether the assent must be documented.

Documentation of Informed Consent

When documentation of informed consent is required, there are two methods available:

1. The subject or the subject's legally authorized representative signs a form (by hand or electronically) containing all the required elements of consent and any additional information necessary to provide complete disclosure. The person who signed the consent form is given a copy as a reference and reminder of the information conveyed.
2. The consent is done orally in language understandable to the subject and is documented by an impartial witness. This process uses two documents: (1) a short form written consent document stating that the required elements of consent have been presented orally to the subject or the subject's legally authorized representative, and (2) a written, IRB-approved summary of what will be said to the subject or the subject's representative. The subject signs the short form. The witness signs both forms. The person actually obtaining consent signs the summary. Copies of the short form and the summary are given to the subject.

Waivers of Documentation

Documentation of the consent process is not always required. Note, however, that waivers of documentation are not waivers of the consent process itself. For waivers of consent, see the criteria noted earlier.

Under the federal regulations at 46.117(c)(1), an IRB may waive documentation under three circumstances:

1. The principal risks are those associated with a breach of confidentiality concerning the subject's participation in the research, and the consent document is the only record linking the subject with the research (e.g., research about women who have left abusive partners)
2. Study participation presents minimal risk of harm to the subject and the research involves no procedures requiring consent outside the context of participation in a research study, for example, a telephone survey.
3. Subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk of harm to subjects, and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Summary

Informed consent includes both the process of sharing information and documenting that the process took place. To ensure that potential subjects can truly make informed decisions about whether to take part in research, issues of comprehension, language, and culture need to be considered in addition to the elements of information provided in the regulations. The regulations provide criteria for waiving any or all of the elements of information and the documentation of consent

Section 6

Populations in Research Requiring Additional Considerations and/or Protections

Adapted from: Block, J. N. & Gordon, B. (n.d.). *Populations in Research Requiring Additional Considerations and/or Protections.* Collaborative Institutional Training Initiative; Hicks, L. (n.d.). *Research with children.* Collaborative Institutional Training Initiative

Introduction

The National Bioethics Advisory Committee defines vulnerable subjects as persons who "have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity…or situational circumstances…or because they are especially at risk for exploitation."

Many of the regulations and discussions in bioethics that surround protecting human subjects in research are reactions to cases now classified as unethical research practices. Many of these cases involved mistreatment of individuals or groups of individuals now referred to as vulnerable populations, or populations requiring additional considerations and/or protections.

In these cases, the research subjects were, for one reason or another, incapable of protecting their own interests. A lack of an ongoing informed consent process contributed to their vulnerability and allowed these events to occur. The events represent a checkered history and might lead one to ask why vulnerable populations are included in research at all.

However, including vulnerable populations is important because in many cases, it is the source of their vulnerability which researchers are attempting to better understand, or to devise ways to mitigate, reduce, accommodate, address, or prevent.

The question of whether to include a vulnerable population in research leads to a more nuanced question, once it has been answered affirmatively that it is permissible to conduct research with the identified group. The next step is to ask whether the research could include a less vulnerable population instead, and still answer the research question. One example is research on children.

The argument in favor of conducting research involving children rests on the consequences of not conducting research involving children in those instances. Such consequences might include the perpetuation of harmful practices, the introduction of untested practices, and the failure to develop new treatments for diseases that affect children. Once the question of whether to include a potentially vulnerable population or those requiring additional protections and/or considerations is resolved, the challenge becomes understanding the details of these groups and their potential vulnerabilities.

Who is Vulnerable?

Individuals may be considered vulnerable because they do not have the decision-making capacity to provide voluntary informed consent, as in the case of children or the cognitively impaired, or because of the situation they are in (such as, being incarcerated or institutionalized). These groups require additional consideration and/or protections. The following examples of groups are often considered vulnerable populations or in need of additional protections or considerations in research:

- Pregnant women
- Human fetuses
- Neonates
- Prisoners
- Children
- Individuals with physical disabilities
- Individuals with mental disabilities or cognitive impairments
- Economically disadvantaged
- Socially disadvantaged
- Terminally ill or very sick
- Racial or ethnic minorities
- Institutionalized persons (for example, persons in correctional facilities, nursing homes, or mental health facilities)

They can also be considered potentially vulnerable because they may not be able to make informed decisions for themselves, they may be in situations in which they can easily be manipulated, or they may be a convenient and readily available study population.

Vulnerable to What?

Before examining the details of certain groups, it is important to understand what one means by the term "vulnerability" as it relates to research. Historically, those who are vulnerable have been subjected to four common types of abuses in human research:

1. Physical control
    a. Subjects who are physically forced to participate in research. This represents a complete lack of voluntariness. When subjects have no choice about whether or not to participate in research, and are under the complete physical control of the researchers.
2. Coercion
    a. The use of a credible threat of harm or force to control another person. This also represents a lack of voluntariness.
3. Undue influence
    a. The misuse of a position of confidence or power to lead or influence others to make a decision they would not otherwise make.
4. Manipulation
    a. The deliberate design and management of conditions or information intended to lead subjects to make a decision they would not otherwise make. Examples of information manipulation are lying, withholding information, or exaggerating

These exist along a continuum of severity with physical control being the most severe and undue influence and manipulation being the least (Nelson & Merz, 2002). However, none of them are appropriate in the context of research on human subjects.

These four abuses can give rise to exploitation, or the action of treating someone unfairly in order to benefit from them in some way. In the context of research, it might be treating subjects in an unfair way in order to benefit from their participation in the research, and using the individual subject merely as a means to conduct the research.

Sources of Vulnerability: Intrinsic Factors and Attributes

Historically, sources of vulnerability are based on an intrinsic factor of an individual or group. This way of understanding sources of vulnerability has affected how the different guidance documents and regulations are written. A common theme is that vulnerability is primarily described as arising from intrinsic factors, characteristics, or attributes of the individual that, when present, confer the label "vulnerable" to the individual or group

The Belmont Report, Section B1: "Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them…The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit"

Declaration of Helsinki, Paragraph 9: "Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence"

Sources of Vulnerability: Situational Considerations

Federal regulations have defined vulnerable populations using a group-based approach. In this way, a child is vulnerable, a pregnant woman is vulnerable, and a prisoner is vulnerable. What this method of classifying vulnerability does not do is account for situations in which an individual might be vulnerable (such as, someone who is acutely ill). Additionally, the group-based classification of vulnerability does not adequately address when an individual has multiple sources of vulnerability (such as, pregnant minors, individuals with mental illness who are also homeless, and other multiple category individuals).

The NBAC provides an alternative way of thinking about and analyzing vulnerability.

1. The NBAC (2001) proposes a more nuanced definition of vulnerability in the context f of research. In general, persons are vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity…or situational circumstances…or because they are especially at risk for exploitation.
2. 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.

Cognitive or Communicative Vulnerability

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. This vulnerability may be thought of in three broad categories. In any of these situations, subjects may not be able to provide fully informed consent to participate in the research.

1. **Capacity-related cognitive vulnerability** - subjects to some extent lack capacity to make informed choices. Examples might include young children, or adults with cognitive impairments that affect decision making.
2. **Situational cognitive vulnerability** - subjects do not lack capacity, but are in situations that do not allow them to exercise their capacities effectively. This might occur when a subject is distracted or during an emergency situation, such as an acute illness or injury.
3. **Communicative vulnerability** - subjects do not lack capacity, but due to limited ability to communicate with the researchers are not able to exercise their capacities effectively. This might include subjects who speak or read different languages than researchers do, or subjects who have speech impairments or difficulty reading.

Institutional Vulnerability

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. Institutional vulnerability may arise when subjects are prisoners, enlistees in the military, employees, or college students when they are required to be research subjects for course credit or when such participation could affect their grades. In these situations informed consent may be compromised because it is not truly voluntary. Further, these individuals may be subject to exploitation because of their subordinate status.

Deferential Vulnerability

Deferential vulnerability is similar to institutional vulnerability, but 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.

Medical Vulnerability

Medical vulnerability arises when prospective subjects have serious health conditions for which there are no satisfactory standard treatments. Such subjects may not be able to adequately weigh the research's risks and potential benefits, and informed consent would therefore be compromised by inadequate comprehension. Further, these subjects are at risk of exploitation because they may overestimate potential benefits. Medical vulnerability may be augmented by the therapeutic misconception when subjects blur the roles played by physician-researchers and fail to appreciate the difference between research and treatment.

Economic Vulnerability

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.

Social Vulnerability

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 and burdens on those groups, and increase the risk of exploitation.

How the Regulations Define and Address Vulnerability

In the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46, there are multiple places where vulnerable populations involved in research are either directly referenced or the reference is implied.

IRB Membership

The HHS regulations contain a number of specific mandates for IRB membership. This includes a specific statement relating to vulnerable populations– if an IRB regularly reviews research that involves vulnerable subjects (such as prisoners), consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects. Due to the nature of it's research, ICJIA's IRB always contains a member that represents prisoner and victim rights.

Criteria for Approval

In the portion of the HHS regulations that describes the necessary criteria for an Institutional Review Board (IRB) to approve research, the following two sections are relevant:

1. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
2. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Types of Vulnerability Defined in the Federal Regulations

HHS at 45 CFR 46.111(b) provides the following list of examples of vulnerable subjects:

- Children
- Prisoners
- Individuals with impaired decision-making capacity
- Economically or educationally disadvantaged persons

The HHS regulations have three subparts that discuss specific additional protections for identified vulnerable populations of individuals when they are going to participate in research. These subparts have been adopted, to varying extents, by some other federal agencies who have adopted the Common Rule (45 CFR 46, Subpart A). Although not a Common Rule agency, the U.S. Food and Drug Administration (FDA), at 21 CFR 56.111(b) (Institutional Review Boards 2015), provides a similar list of vulnerable subject examples.

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Embryos and fetuses are vulnerable because they have no capacity and are under the direct control of their mother. Though the regulations imply that the pregnant women herself is vulnerable (perhaps because of the unique dependent relationship with the fetus, not all commentators agree) (Schonfeld, 2013).

Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Prisoners have their rights limited in some way. They are under direct control of the state to varying extents, and so may be subject to coercion. They may see participation in research as a way to improve their existence in prison, and therefore may be subject to undue influence. They also live in situations that are markedly different from the rest of society, and they may be undervalued as a social group. They may feel they have to take part in research to improve their existence in prison or to be eligible for parole. They are a convenience population, and by being incarcerated, they do not have the choice or ability to leave the prison.

Definition of Prisoner

The federal regulations defines prisoner as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

When a Subject Becomes Incarcerated After Study Enrollment

If a study requires a follow-up visit with a subject who has become incarcerated during the course of research, the advised course of action is to delay re-contacting the subject until they have been released. If a study necessitates visiting a subject while they are incarcerated a detailed amendment must be submitted to the IRB.

Composition of IRB When Prisoners are Involved

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

- A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

Additional IRB Duties When Prisoners are Involved

1. The research under review represents one of the categories of research permissible under §46.306(a)(2) [discussed later]
2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
3. The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
5. The information is presented in language which is understandable to the subject population;

6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7. Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.
    a) The Board shall carry out such other duties as may be assigned by the Secretary.
    b) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

Permitted Research Involving Prisoners (§46.306)

1. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
2. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
3. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
4. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

Subpart D: Additional Protections for Children Involved as Subjects in Research

Children have a wide range of capacities based on age, developmental stage, maturity, and psychological state. They may be vulnerable to control, coercion, undue influence, and manipulation by others. These others may include parents or guardians, researchers, teachers, and others. Due to their age, children may face legal limitations (for example, not lawfully able to leave home, seek employment, or make their own medical decisions) because they are not able legally to make their own decisions until they reach the age of majority in many circumstances.

Legally Authorized Representative (LAR)

When a subject cannot consent for themselves, researchers may obtain consent from a LAR when appropriate. The HHS regulations define LAR as, “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research.”

Defining Children

According to the federal regulations, children are persons who have not yet attained the legal age of consent under the applicable laws in the setting in which the research will take place. Generally, though not always, the age of consent is the age at which minors reach the age of majority and are considered adults.

In the U.S., state law dictates the age of majority. In most, but not all states, the age of majority is 18. This means that a 17-year-old may be considered a child when applying the federal regulations for protecting research subjects. In Alabama and Nebraska, the age of majority is 19 and in Mississippi it is 21. Some states have a legal process of emancipation that confers adult status on those who are younger than the age of majority. The conditions under which children may be released from parental authority vary by state. In some states, emancipated minors may have the legal authority to provide permission for their own children to become research subjects, but may not be able to consent for themselves unless an Institutional Review Board (IRB) waives the requirement for parental permission.

The age of majority may be quite different in other countries. It also is possible that a country may have no legal definition of "majority." In such cases, researchers have to rely on community standards and practices to determine whether subjects are considered children or adults.

Regulations That Apply to Research with Children

There may be many layers of regulations and policies when children are involved as subjects in research, including federal regulations, state and local law, and institutional policies.

1. The basic federal regulations for protecting research subjects, known as the Common Rule (45 CFR 46, Subpart A), have been adopted by numerous federal agencies and departments.
2. The provisions of Subpart D, of the HHS regulations, "Additional Protections for Children Involved as Subjects in Research."
3. State and local law, and institutional policy, as applicable. For example, provisions for waiving parental permission for neglected or abused children cannot violate federal, state, or local law.

The provisions of Subpart D must be applied to all research funded by U.S. Department of Health and Human Services (HHS). However, some federal agencies have agreed to apply the provisions of the Common Rule to research with human subjects, but not the provisions of Subpart D. In that case, institutional policies will regulate research with children. It is important to always check with the reviewing IRB and the institutional policy for research involving children as subjects.

Subpart D includes:

1. Restrictions on the applicability of the criteria for exemption when children are the subjects
2. A hierarchy of four levels of risk and associated benefits
3. Specifications for parental permission and child assent requirements at each level
4. Criteria for waivers of parental permission and child assent

Exempt Research with Children as Subjects

The Common Rule describes activities that meet the definition of research with human subjects but are not subject to the provisions of the rule. Subpart D restricts the use of exemptions with children as subjects. Only Exempt Categories 1, 4, 5, 6, 7, and 8 may be applied to research subject to Subpart D if the conditions of the exemption are met.

Exempt Category 2 parts (i) and (ii) may only apply for research involving educational tests or observation of public behavior when the investigator does not participate in the activities being observed. Exempt Category 2 part (iii) may not be applied to research subject to Subpart D, nor may Exempt Category 3 (research involving benign behavioral interventions with adults).

Limitations to Exempt Research

Exempt Category 2 under parts (i) and (ii) can be used for research with children under specific circumstances. Limitations for Category 2 research subject to Subpart D include:

- Research activities are limited to educational tests and observation of public behavior
- If the research involves observation of public behavior, the researcher does not participate in the activities being observed
- Research approved with a limited IRB review under part (iii) of Category 2 (which involves recording information in such a manner that the identity of the subjects can be readily ascertained) is not permitted

Research involving benign behavioral interventions (Category 3), in conjunction with the collection of information, cannot be exempt for children as it is applicable only for adult subjects.

Expedited Review When Children Are Subjects

Expedited review is an option when the research activities pose no more than minimal risk to subjects and fall within one or more of the explicitly defined categories of activity.

With the exception of limits on the amount and frequency of blood that may be drawn from children, there are no regulatory restrictions on using the expedited review process when children (minors) are subjects.

Parental Permission and Child Assent

By definition, children are unable to provide informed consent to participate in research. The basic model when working with children is that parents (or legal guardians) provide permission for their children (or wards) to participate in research and then subsequent to the parental permission the researcher contacts the children. Children then provide their assent to become subjects. Assent is a child’s affirmative agreement to participate. The absence of dissent should not be construed as assent when the child is old enough that assent is meaningful. Generally, parental permission can only override a child's dissent when the health of the child is at stake.

Although particulars vary, it generally is assumed that children have limited rights to decide what will happen to them, based on their age and maturity. At one end of the age and maturity continuum are infants and toddlers, who are not capable of making a decision about whether to participate, although they may communicate their dissent if they become distressed. At the other end of the continuum are older adults who are capable of both making a decision and actively assenting or dissenting to participate in research.

No guidelines can replace a researcher's knowledge about the children to be recruited for a study. Researchers should be prepared to support their proposed assent process either with data or experience-based evidence, particularly if the children involved have vulnerabilities other than their youth, or live in a country, community, or society unfamiliar to the IRB.

Child Assent

Federal regulations specify what kinds of information should be included in an adult consent process. Subpart D notes that the same kinds of information should be provided to parents when asking them to provide permission for their children to be research subjects. However, there are no regulations about the content of the child assent process.

A number of factors should be considered when developing child assent processes, including the proposed research activity and the age and maturity of the children involved. When research activities involve adolescents, whose capacity to understand resembles that of adults, the assent procedure should be similar to informed consent procedures designed for adults. If children's age and maturity level limit their ability to fully comprehend the nature of the research activity, but they are still capable of being consulted about participation in research, the assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve

If a study involves children of different ages, appropriate assent processes need to be developed for each age group.

Cultural Differences

Researchers may need to take into account the nationality, ethnicity, and socioeconomic status of their potential subjects in order to design appropriate parental permission and child assent processes.

Cultural assumptions about the rights of children vary widely. In some countries or subgroups, it may be inappropriate and perhaps offensive to ask children to make research-related decisions.

Longitudinal Studies

In order to respect the emerging maturity and autonomy of children and adolescents in longitudinal studies, some researchers advocate revising the child assent process as the child grows older, providing more detail about the study, and rearming assent. Once children reach the age of majority they may sign a consent form for adults.

Risk Level, Parental Permission, and Child Assent

As the risk level of the research increases, Subpart D has increasing requirements for parental permission and child assent.

Subpart D divides research with children into four categories of risk and related benefits. Each category carries specific review requirements, as well as parental permission and child assent requirements. As levels of risk increase and benefits to individual children decrease, review criteria become more stringent, and the requirements for permission and assent increase.

Category	Parental Permission / Child Assent Requirements	Risk/Potential Benefit to Child
46.404	At least one parent*	No more than minimal risk
46.405	At least one parent*	Greater than minimal risk with the prospect of direct benefit
46.406	Both parents**	Greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
46.407	Both parents**	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

* The IRB may find that permission of one parent is sufficient.
** Research falling under 46.406-7 requires permission to be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Note: The IRB shall determine that adequate provisions are made for soliciting the child's assent, when in the IRB's judgment the child is capable of providing assent.

Wards

When the research includes children who are wards of the state or any other institution or entity, there are additional considerations required by HHS regulations. Pursuant to 46.409, before wards can be included in research that is greater than minimal risk and approved by an IRB pursuant to 46.406 or 407 (and referred to the Secretary of HHS if under 407), it must meet the following conditions:

- The research must be either related to the children's status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.
- The IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

State laws and institutional policies may dictate additional protections for wards as well.

Documentation of Parental Permission and Child Assent

IRBs have the authority to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child's age, maturity, and degree of literacy, the IRB should decide what form of documentation, if any, is most appropriate. If adolescents are involved in research where a consent form would have been used if the subjects were adults, it generally would be appropriate to use a similar form to document an adolescent's assent. If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place.

Documentation of parental or guardian permission for children to become research subjects is required unless waived by an IRB in accordance with the regulations.

Waivers of the requirement to document parental or guardian permission may be approved by an IRB in accordance with the same regulations that govern waivers of the requirement to document adult consent.

Therefore, such waivers may be permitted under the following three conditions:

- The documentation of consent (informed consent form) is the only record linking the child to the research, and the principal risk would be potential harm resulting from a breach of confidentiality. If subjects wish to have a signed consent form, their wishes will govern.
- The research presents no more than minimal risk of harm and involves no f procedures for which consent is normally required outside the research environment.
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects, and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

When the requirement for documentation is waived, the IRB may require the researcher to present each subject (or parent or guardian) with a written statement regarding the research.

Waivers of Parental Permission and Child Assent

An IRB may waive the requirement to secure child assent if either:

1. The capability of some or all of the children is so limited that they cannot reasonably be consulted.
2. The intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.

The IRB may also waive the assent requirement if the research meets the same criteria as for waivers of informed consent for adults.

The same criteria may be used for waivers of the requirement to secure parental permission.

Both the Common Rule and Subpart D include provisions for waiving the requirement to secure parental or guardian permission if an IRB determines that the research is designed for conditions or for a subject population for which permission is not a reasonable requirement to protect the subjects. However, an appropriate mechanism must be in place to protect the children and the waiver needs to be consistent with federal, state, or local law. For example, an important area of inquiry is why and how certain teenagers come to live on the streets. An anthropologist wishing to interview teenagers who are runaways or who have severed ties with their families could not do so if parental permission was required.

It is also important to note that there are different criteria for a public benefit or service program.

An Expanded View of Vulnerability: Examples of Additional Vulnerabilities Not Explicitly Covered by the Federal Regulations

There exists a diversity of individuals, groups, or situations that may render individuals vulnerable in the context of research, even though they are not identified specifically in the regulations and given specific additional protections. The following are some examples that are important to understand and consider when thinking about research involving vulnerable populations or those requiring additional protections and/or considerations.

Vulnerability Due to Critical Illness

Vulnerability for the group of critically ill individuals and in the situation of emergency research may be due to intrinsic factors (like altered decision-making capacity, and reduced capacity to consent) and situational factors (like coercive settings, or undue influence and inducements).

Critically ill individuals may have limitations in their ability to process information, make complex decisions, and communicate their wishes. This may lead to them being in a state of diminished capacity to make autonomous decisions and protect their own interests.

Even if potential subjects are able to understand and communicate their wishes, the voluntariness of their decision can be affected by situational factors, such as those present in emergency research. If the treating physician also occupies the role of researcher, this may unduly influence an individual's willingness to participate in research.

Vulnerability Due to Terminal Illness

Persons at the end-of-life may be vulnerable for numerous reasons, including cognitive and physical impairments, which may progress as death approaches. Threats to voluntariness may arise as a result of an often desperate desire for relief from pain and suffering, presenting the risk of exploitation. Desire to please caregivers may be particularly prominent. In addition, the risks and benefits that are important to patients near the end-of-life may be much more difficult to define. In other words, an individual's goals and perceptions of burden and risk may change substantially as he or she nears death.

Vulnerability Due to Decisional Impairment

It is important to recognize that decisional impairment can result from a variety of intrinsic factors and situational conditions, and is not limited to individuals with a psychiatric diagnosis. Decisional impairment exists along a spectrum and therefore must be assessed in the context of the information that must be understood and the nature of the decisions to be made. Decisional impairment can result from many causes including stroke and other Central Nervous System (CNS) disorders, trauma, medical treatment, and substance abuse. In a number of cases, decisional impairment can result from a documented disability that is protected under the Americans with Disabilities Act (ADA) (Equal Opportunity for Individuals with Disabilities 2009).

Decisional impairment is often compounded by situational factors that limit freedom of choice and the ability to understand the nature and consequences of research participation. Some examples include:

- Stigma
- Lack of or insufficient healthcare insurance coverage
- Under-education
- Discrimination
- Institutionalization
- Homelessness
- Inadequate access to housing

Vulnerability Due to Physical Disabilities or Impairments

Physical disabilities and impairments can result in diminished participation in society because the disability limits a major life activity (Equal Opportunity for Individuals with Disabilities 2009). The diminished participation in society can lead to vulnerability both because of an intrinsic factor (such as, a physical limitation the individual experiences), or a situational factor (such as, a lack of an adequate accommodation for the disability allowing for full participation). Intrinsic factors such as a limitation in one of the senses (like sight) can lead to a very f strong desire to participate in research that may have the prospect of direct benefit to the subject, which potentially leads to undue influence. Additionally, situational factors in the study design can lead to vulnerability. For example, not providing a large-print or Braille consent form to an individual who is visually impaired or blind can interfere with the voluntariness of consent.

Vulnerability Due to Economic Disadvantage or Social Marginalization

Economically disadvantaged individuals are those who are under-resourced to provide for themselves or their families, and experience particular hardships due to disparities and inequalities in the society in which they live. These situational factors can affect or limit the subject's voluntariness to participate in research.

Socially marginalized individuals are those who lack influence in society or standing for a socially constructed reason (such as, race, religion, or disease state). Individuals who are socially marginalized often lack adequate access to social organizations such as the legal system.

The potential for undue influence or manipulation is higher for these subjects. For example, the prospect of getting monetary compensation for participation in research could significantly affect the willingness to participate, influencing the subject to accept greater risks of harm than they would otherwise accept. Economically disadvantaged individuals may also enroll in health research because it could mean access to healthcare where they may not otherwise have access.

Vulnerability Due to Social Hierarchy

Hierarchical social structures are found in situations throughout society. Examples include:

- Hospitalized individuals
- Nursing home residents
- Students
- Employees
- Prisoners
- Soldiers
- Other military personnel
- In some cases ethnic groups (such as, indigenous populations)

Hierarchical structures have the potential to create issues centered around power/control, coercion, undue influence, and manipulation. The "higher" hierarchical individual has the ability to exercise their power or control over others (subordinates) in some way that is either real or perceived. Examples include:

- Program directors seeking enrollment in research from residents they directly supervise
- Faculty members recruiting students they currently teach
- Commanding officers seeking enrollment in research from soldiers or military personnel that report to them through the chain of command

Sexual and Gender Minority (SGM) Status

“Sexual and gender minority” is an umbrella phrase that encompasses lesbian, gay, bisexual, and transgender populations as well as those whose sexual orientation, gender identity and expressions, or reproductive development varies from traditional, societal, cultural, or physiological norms. Members of SGM communities may be vulnerable to discrimination, bullying, violence, and prejudice. Gender differences in societal structures, usually directed towards women, may render one gender vulnerable to these forces as well. SGM individuals face social and cultural vulnerabilities because many have experienced some forms of prejudice and discrimination at home, school, work, and/or other social contexts or organizations due to their sexual orientation. Gender differences may also make some individuals vulnerable, especially in areas of the world where women do not have the basic rights of citizenship (access to an education, the right to divorce, franchise). These vulnerabilities can lead to increased risks of harm to the individuals in their participation in research, and the prospect of undue influence or manipulation.

The principle of beneficence or "do no harm" is particularly important in SGM research, and social and behavioral researchers must be cognizant of potential harm that could be associated with study participation and institute safeguards to minimize potential risks of harm when conducting research with SGM subjects experiencing additional vulnerabilities.

Vulnerability Due to Uncertain Immigration Status and Individuals Involved in Illegal Activities

Individuals or groups of people who are regarded as being involved in illegal activities or are undocumented immigrants may be vulnerable because of the potential consequences that exposure may have to them. This can include risks of retaliation against them by others and legal consequences.

The risks of harm are higher with these individuals, and can often include group-based risks of harm, such as violating the trust of a portion of society that can have negative public health consequences. For example, if undocumented individuals or those involved in illegal activities fear that they will be exposed when seeking medical care, they may not seek medical care when they need it. This can result in heightening public health consequences for that group of individuals.

Research Ethics Implications

The three pillars often described in research ethics (respect for persons, beneficence, and justice from the Belmont Report) are important to examine in the context of vulnerable individuals or groups participating in research. A combination of intrinsic factors and situational conditions that lead to vulnerability also open up the individual or group to potential problems that interfere with one of the pillars, requiring attention by an IRB and potentially additional safeguards being put in place in the research.

Autonomous Decision Making (Respect for Persons)

There is the possibility that due to intrinsic factors or situational conditions individuals or groups can be open to coercion or undue influence. The National Commission (1977) asserts that coercion occurs when one person intentionally presents an overt threat of harm in order to obtain compliance. An example would be a professor telling students, "participate in my research or you will fail the class." Similarly, a physician threatening to abandon a patient who refuses to participate in a study represents coercion. However, the National Commission's definition may be too narrow, as coercion need not be overt. For example, a patient who participates in a study run by his/her primary f care physician, because the patient fears his/her care is contingent on participation, is reacting to fear of retribution (coercion) (whether the physicians intends this or not).

Inducements, in contrast, 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 USD may be acceptable for an hour-long research study; offering $1,000 USD, 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 research's risk-benefit relationship.

Misunderstanding of the research is also a problem that can interfere with autonomous decision making. For individuals or groups who are vulnerable, the prospect of direct benefit, whether real or perceived, can dramatically affect the individual's voluntariness. This can lead to a person accepting a much higher level of risk of harm than they otherwise would accept, or subscribing to the false belief that the research may hold out the prospect for direct benefit to them.

Beneficence

The concept of beneficence in research includes weighing the research's risks of harm against the benefits. When conducting research involving vulnerable individuals or groups, two issues arise related to risks of harm.

1. There may be changes in the magnitude of an already identified risk of harm due to the vulnerability experienced by the individual or group.
2. There may be previously unrecognized risks of harm that arise because of the vulnerability experienced by the individual or group.

Justice

There are three issues that may arise when considering issues of justice in research involving vulnerable individuals or groups.

1. In some types of research, a vulnerable group may be the primary group on which the research is conducted because the investigation is focused on the source of vulnerability. This means that the research burden is heaviest on the group based solely on the presence of their vulnerability. This also could mean that those who experience this vulnerability may be the primary beneficiaries of the research results. What is important here is to be cognizant of the concept of justice in the Belmont Report. Therefore, it is important to remain mindful of the potential disparity in burden the group faces on account of this, noting that it may be acceptable.
2. Some individuals or groups who are vulnerable may become the study focus merely for ease or convenience of access, or because risks of harm or burdens to them are trivialized, as the group is undervalued. This is a significant issue and should be monitored carefully. There are historical cases of prisoners or wards of the state being studied because of convenience when there were more appropriate study groups to enroll. This was the case for both the Jewish Chronic Disease case and the Willowbrook case. In this instance, researchers enrolled populations that were both undervalued by society and convenient for them to study.
3. Designing studies to exclude individuals or vulnerable groups from the research because of the complications and additional requirements for studying them is problematic (either real or perceived). In this case, the lack of inclusion hurts the ability to advance understanding and the underlying science, and denies the group the potential benefit of research.

Guidance for IRBs and Reviewers

The breadth of the expanded view of vulnerability described here and the complication involved with adhering to the regulations combined with a common sense approach to try to protect subjects, result in increased difficulty in the IRB's review of research. Therefore, a stepwise approach to consideration of the research proposal may be helpful.

Are subjects vulnerable?

It is important to ask researchers to fully describe the population to be studied and the situations in which the potential research subjects and 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. It will also help the IRB and researchers quickly identify if there are any regulations that must be applied. Researchers generally have a much clearer understanding of the circumstances and potential challenges their research subjects face. They are in a unique position to share their insight. When IRB's request this information, it facilitates the review of research and in the best circumstances leads to better designed research studies, improved review of research, and better protection of human subjects. Researchers and IRBs should consider:

- Is there a power differential between researchers and subjects?
- Are there potential excessive motivating factors for subjects?
- Are there potential communication issues for subjects?
- Are there potential decisional issues for subjects?
- Is the recruitment process acceptable?
- Are advertisements acceptable?
- Are there economic issues that might affect the acceptability of payment arrangements?

Is inclusion of vulnerable subjects appropriate?

As discussed above, if some potential subjects are vulnerable, the IRB must then decide if inclusion of this population is indeed appropriate. The IRB must consider the competing ethical imperatives of respect for persons (and especially protection of persons who lack self-determination and require protection), and of beneficence and justice (offering a fair opportunity to benefit from participation).

Are vulnerable subjects adequately protected?

If the inclusion of vulnerable subjects is appropriate, does the research plan (including subject identification, recruitment, and consent) minimize the possibility of coercion, undue influence, manipulation, and exploitation? Meanwhile, does the research plan maximize the likelihood of valid informed consent? At a very minimum, is the process of informed consent valid? That is, is information presented in an understandable manner, do subjects comprehend the details of the research and their rights as research subjects, and is the process of consent conducive to true voluntariness?

Many of the previously noted questions are still relevant. In addition, researchers and IRBs should consider:

- Are there reasonable accommodations provided for subjects who may be disabled?
- Is information presented to subjects in an understandable and accessible manner?
- Do subjects comprehend the research details and their rights as research subjects?
- Is the consent process conducive to true voluntariness?
- Who is involved in the consent process?
- Can the subject consent for him or herself?
- Do the vulnerabilities of the subjects require the additional protections of a research subject advocate?

It is important to remember that the review process described here is an iterative process. Adequate protections may now allow inclusion of a population previously considered too vulnerable, or indeed may make a population not vulnerable at all.

Summary

Vulnerability may be considered in terms of categories (children, fetuses, persons who are cognitively impaired, persons who are economically disadvantaged, and so on) based on intrinsic characteristics of group members. The National Bioethics Advisory Committee (NBAC) proposed a more nuanced description as persons "who have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity…or situational circumstances…or because they are especially at risk for exploitation," and classified vulnerabilities more broadly as cognitive or communicative, institutional, deferential, medical, economic, or social.

Considering this broader NBAC view, many more types of vulnerability can be recognized as having difficulty providing informed consent, or being at risk for exploitation. These groups are described above.

These vulnerabilities ultimately relate to challenges to the ethical principles underlying human subjects research:

- Autonomous decision making (respect for persons)
- Beneficence
- Justice

Researchers and IRBs must carefully consider characteristics of the subject populations and situational factors to determine if there are potential vulnerabilities, and if so, whether there is adequate justification to include these persons in the research and what additional protections may be required. Regarding this last consideration, researchers and IRBs must consider the risk of harm to individual subjects and populations if they are excluded from participation.

It is important for researchers and IRBs to evaluate the selection of subjects, taking into consideration the purpose of the research and the setting in which it will take place. They must examine the risks of harm and benefits to vulnerable populations included in research and ensure that provisions to protect them are in place.

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