There are pending regulatory changes that have a general compliance date of 21 January 2019. This module will be updated in January 2019 to reflect these changes. We invite you to review the **CITI Program's Final Rule Resources** for information on the changes to the Common Rule.

POPULATIONS IN RESEARCH REQUIRING ADDITIONAL CONSIDERATIONS AND/OR PROTECTIONS

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INTRODUCTION

The National Bioethics Advisory Committee (NBAC 2001) 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. Some case examples include:

- Jewish Chronic Disease Hospital Study
- U.S. Public Health Service Study (Tuskegee Study of Untreated Syphilis in the Negro Male)
- Nazi Medical War Crimes (Nuremberg Trials)
- Tearoom Trade Study
- Willowbrook Hepatitis Study

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 above examples are discussed in the CITI Program modules *History and Ethics of Human Subjects Research* and *History and Ethical Principles - SBE*. 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 (The National Commission 1977).

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.

Learning Objectives

By the end of this module, you should be able to:

- Describe the different sources of vulnerability.
- Distinguish between vulnerable populations in research who are specifically protected in the federal regulations and those who are not.
- Identify additional protections for vulnerable populations who are not specifically protected in the federal regulations.
- Explain the effect on autonomy, beneficence, and justice that may arise due to research on vulnerable individuals or groups.

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). 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)

These groups require additional consideration and/or protections. 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.

Common Types of Abuses In Human Research	
Type of Abuse	**Explanation**
Physical Control	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.
Coercion	The use of a credible threat of harm or force to control another person. This also represents a lack of voluntariness.
Undue Influence	The misuse of a position of confidence or power to lead or influence others to make a decision they would not otherwise make.
Manipulation	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 and Merz 2002, V69-80). 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.

INTERNATIONAL COUNCIL ON HARMONIZATION - GOOD CLINICAL PRACTICE (ICH-GCP), SECTION 1.61

"Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate" (ICH 2017).

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" (The National Commission 1979).

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" (WMA 2013).

CIOMS, COMMENTARY ON GUIDELINE 15

“In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests. This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests” (CIOMS 2016).

A common theme in the excerpts above 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.

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 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 benefit. 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 (Protection of Human Subjects 2009), there are multiple places where vulnerable populations involved in research are either directly referenced or the reference is implied.

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.

45 CFR 46.111

(a)(3) 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 involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

This specifically names a few categories of potentially vulnerable populations or groups requiring additional protections and/or considerations. Later in the regulations (in Subparts B, C, and D), three of these populations -- prisoners, pregnant women, and children -- and their additional protections are described in detail.

IRB MEMBERSHIP

The HHS regulations contain a number of specific mandates for IRB membership. This includes a specific statement relating to vulnerable populations.

45 CFR 46.107(A)

If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

This statement highlights the importance of specifically considering and providing

additional protections and/or considerations for vulnerable populations participating in research.

TYPES OF VULNERABILITY DEFINED IN THE FEDERAL REGULATIONS

HHS at 45 CFR 46.111(b) (Protection of Human Subjects 2009) and the U.S. Food and Drug Administration (FDA) at 21 CFR 56.111(b) (Institutional Review Boards 2015) provide the following list of examples of vulnerable subjects:

- Children
- Prisoners
- Pregnant women
- Handicapped
- Mentally disabled persons
- 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 (Subpart A).

SUBPART B. ADDITIONAL PROTECTIONS FOR PREGNANT WOMEN, HUMAN FETUSES AND NEONATES INVOLVED IN RESEARCH (45 CFR 46.201-7)

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, 189-206).

SUBPART C. ADDITIONAL PROTECTIONS PERTAINING TO BIOMEDICAL AND BEHAVIORAL RESEARCH INVOLVING PRISONERS AS SUBJECTS (45 CFR 46.301-6)

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.

SUBPART D. ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECTS IN RESEARCH (45 CFR 46.401-9)

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.

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 (RESEARCH AT THE END-OF-LIFE)

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 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

GENDER OR SEXUAL MINORITY STATUS

Members of the gender and sexuality diversity (GSD) community 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. GSD 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 GSD 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 GSD 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 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?


Ask
Tell

It is important to ask researchers to fully describe the population to be studied and the situations in which the potential research subjects find themselves. This should answer both the question about the intrinsic factors or attributes, as well as the situational forces that may give rise to different types of vulnerability. 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.

Populations in Research Requiring Additional Considerations and/or Protections

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 NBAC (2001) 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.

REFERENCES

- Council for International Organizations of Medical Sciences (CIOMS). 2002. "**International Ethical Guidelines for Health-related Research Involving Humans**." Accessed February 7, 2017.
- Equal Opportunity for Individuals with Disabilities, 42 USC § 126 (2009).
- Institutional Review Boards, 21 CFR § 56 (2015).
- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 2017. "**ICH Harmonised Guideline: Integrated Addendum to ICH E6 (R1): Guideline for**

Good Clinical Practice E6(R2)." Accessed March 2, 2016.

- National Bioethics Advisory Commission (NBAC). 2001. "Ethical and Policy Issues in Research Involving Human Participants: Volume 1 – Report and Recommendations of the National Bioethics Advisory Commission." Accessed March 2, 2016.

- Nelson, Robert M., and Jon F. Merz. 2002. "Voluntariness of consent for research: an empirical and conceptual review." *Medical Care* 40(9):V69-80.

- Protection of Human Subjects, 45 CFR § 46 (2009).

- Schonfeld, Toby. 2013. "The perils of protection: vulnerability and women in clinical research." *Theoretical Medicine and Bioethics* 34(3):189-206.

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1977. "Report and Recommendations: Research Involving Children." Accessed March 2, 2016.

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." Accessed March 2, 2016.

- World Medical Association (WMA). 2013. "WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects." Accessed March 2, 2016.

ADDITIONAL RESOURCES

- U.S. Food and Drug Administration (FDA). 2018. "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials." Accessed April 12, 2018.

Original Release: August 2014
Last Updated: June 2017

Take the quiz for Populations in Research Requiring Additional Considerations and/or Protections

View Post-Course Completion Options
