



Vulnerable Populations Background

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I. Purpose and Design of this Module

The Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) conducts research and develops reports and other materials for public distribution in order



to advise the President of the United States on bioethical issues that arise as a consequence of advances in biomedicine and related areas of science and technology. To support ethics education and facilitate the integration of bioethical analysis into existing curricula across traditional and nontraditional educational and professional settings, we have developed pedagogical materials designed to increase distribution of the Bioethics Commission's work and to facilitate easy access to the material in its reports by professors, instructors, teachers, and professional leaders (collectively "instructors").

This module was prepared for instructors who want to include in their teaching a discussion of ethical issues related to research involving vulnerable populations. It provides foundational information, ethical reasoning, applications, questions, discussion points, and additional readings that are designed to give the instructor enough information to plan lectures, discussions, or activities. These materials are not intended to be a lecture script or outline, but rather to support the instructor in developing his or her own presentation(s).

In addition to the background information provided here, further modules provide a guide for instructors to facilitate incorporation of the Bioethics Commission's published reports as a resource for teaching and discussion. The featured Bioethics Commission reports illustrate relevant and current issues concerning vulnerable populations in the research context.

Instructors are invited to use these materials, or any portion of them, to integrate bioethics into coursework and professional development activities in all disciplines. Feedback is welcome, including insight into how the materials have been used and suggestions for how they might be improved for use in the future. (Send feedback to Education@bioethics.gov.)

II. Introduction

Vulnerability means that an individual or groups of individuals lack the ability to fully and independently protect their own interests and so are vulnerable to being harmed or wronged.¹ In the context of human subjects research, vulnerability is often understood to stem from a person's inability or impaired ability to give ethically or legally valid informed consent, or from a situation or circumstance, such as severe illness, economic disadvantage, or incarceration, that puts an individual or group of individuals at greater risk of being exploited or unfairly taken advantage of in the research setting.

¹ Schroeder, D., and E. Gefenas. (2009). Vulnerability: Too vague and too broad? *Cambridge Quarterly of Healthcare Ethics*, 18, 113-121; Levine, C., et al. (2004). The limitations of "vulnerability" as a protection for human research participants. *American Journal of Bioethics*, 4(3), 44-49.



The history of human subjects research contains many examples in which vulnerable populations were exploited in the name of science. Notable among these are the Nazi experiments conducted on prisoners without their consent during World War II, and the U.S. Public Health Service Study of Untreated Syphilis in the Male Negro, Macon County, Alabama (the syphilis studies in Tuskegee), in which poor African American men with syphilis were left untreated for nearly 30 years while researchers observed the progress of disease.² In these cases, as well as others described in this module, individuals who were unable fully to protect their own interests were exploited to benefit others. Recognition of these research abuses led to the creation of codes of conduct, guidelines, and regulations for human subjects research generally, and vulnerable populations specifically.³ As a result, current federal regulations, international codes, and scholarship in research ethics acknowledge that research involving vulnerable populations raises unique ethical issues requiring special attention.

The Syphilis Studies in Tuskegee

The syphilis studies in Tuskegee were conducted in Alabama between 1932 and 1972 and involved nearly 400 impoverished African American men with syphilis (and 200 without the disease). The men with syphilis were left untreated for nearly 30 years, despite the availability of antibiotics to treat the infection for some of that time, while researchers observed the progress of the disease. Researchers selected this population for the study because of a high prevalence of syphilis, and because of their interest in studying the progress of the disease among African Americans. They presumed that African American men typically would not seek or continue treatment for the disease. In exchange for participation, the men were given free medical exams, free meals, and burial insurance. They were never told they had syphilis; rather were told they were being treated for “bad blood.” The design and conduct of this research exploited the vulnerability of the men who participated by deceiving them about the nature of their disease, withholding treatment, and putting them at considerable risk without any appropriately compensating benefit. The research has been condemned widely as a profound violation of the principles of research ethics.

Sources: Centers for Disease Control and Prevention (CDC). (2013). U.S. Public Health Service Syphilis Study at Tuskegee: The Tuskegee Timeline; Jones, J.H. (1993). *Bad Blood: The Tuskegee Syphilis Experiment*. New York, NY: The Free Press; Presidential Commission for the Study of Bioethical Issues. (2011, December). *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, pp. 82-83; Brandt, A.M. (1978). Racism and research: The case of the Tuskegee Syphilis Study. *Hastings Center Report*, 8(6), 21-29.

² Jones, J.H. (1993). *Bad Blood: The Tuskegee Syphilis Experiment*. New York, NY: The Free Press.

³ Centers for Disease Control and Prevention (CDC). (2013). U.S. Public Health Service Syphilis Study at Tuskegee: How Tuskegee Changed Research Practices. Retrieved August 14, 2014 from <http://www.cdc.gov/tuskegee/after.htm>.



The Bioethics Commission has analyzed issues that arise in research involving vulnerable populations, including the U.S. Public Health Service’s studies involving the intentional exposure of several vulnerable Guatemalan research subject populations to disease without their consent, and the ethical issues in conducting medical countermeasure research with children.⁴

This module introduces the reader to ethical issues that arise when research is conducted with vulnerable populations, including children, individuals who are decisionally impaired due to conditions such as advanced dementia or some forms of mental illness, prisoners, and participants in international research. These populations require special protections as research participants for both ethical and historical reasons, including the potential for exploitation and the challenges of obtaining informed consent as a means of respecting participant autonomy. This module discusses how vulnerability is defined; explores historical examples of exploitation of vulnerable populations in research; describes ethical principles applicable to research with vulnerable populations; and describes national and multinational regulations, codes, and guidelines that address research with vulnerable populations.

III. Learning Objectives

Students should be able to:

1. Define and discuss the term “vulnerable population” in the context of human subjects research.
2. Understand the ethical considerations relevant to research with vulnerable populations.
3. Understand existing U.S. regulations and multinational guidelines that govern research with vulnerable populations, and their historical context.
4. Explain why and how research with vulnerable populations can be conducted ethically and can be of benefit to those populations.

⁴ Presidential Commission for the Study of Bioethical Issues. (2011, September). *“Ethically Impossible” STD Research in Guatemala from 1946-1948*. Washington, DC: PCSBI; Presidential Commission for the Study of Bioethical Issues. (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSBI.



IV. Background

A. Defining Vulnerability

The word vulnerability stems from the Latin *vulnerare*, which means to wound. In the context of human subjects research individuals or groups are vulnerable if they are unable fully and independently to protect their own interests, either due to intrinsic characteristics (e.g., age or immaturity), or circumstances (e.g., illness, incarceration, or poverty). It is a central tenet of the ethics of human subjects research that additional steps be taken to protect vulnerable participants from harm. For example, the U.S. Code of Federal Regulations requires that institutional review boards (IRBs) approve research involving vulnerable participants only when “additional safeguards have been included in the study to protect the rights and welfare of these subjects.”⁵ The World Medical Association’s *Declaration of Helsinki* states that vulnerable groups and individuals “should receive specifically considered protection.”⁶

Determining which individuals or groups should be considered vulnerable and in need of additional protections as research participants is an ongoing challenge for researchers and IRBs. There are different approaches to defining vulnerable populations that might be appropriate in different contexts. These include the categorical (or subgroup) approach, and the contextual approach.

1. Categorical Vulnerability

The categorical (or subgroup) approach defines vulnerable populations as those groups in society whose members share features that might make them vulnerable. For example, the U.S. Code of Federal Regulations lists “children, prisoners, pregnant women, mentally disabled persons, [and] economically or educationally disadvantaged persons” as vulnerable groups.⁷

The categorical approach is most applicable when all members of a particular group are vulnerable for the same reason. For example, although children vary considerably in their levels of maturity, all children are vulnerable because they lack the fully developed capacity for autonomous decision making that comes with developmental maturity. The categorical approach is more contentious, however, when a person’s vulnerability results not from an intrinsic characteristic that makes them unable to protect their own interests (e.g., immaturity in the case of children), but from circumstances (e.g., poverty, illness, or social marginalization) that affect individuals differently and might make some members

⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. §46.111(b).

⁶ World Medical Association (WMA). (2013). World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *Journal of the American Medical Association*, 310(20), 2191-2194.

⁷ *Protection of Human Subjects, HHS*. 45 C.F.R. §46.111(b).



of a group more vulnerable to exploitation.⁸ For example, while a number of regulations include the “economically disadvantaged” as a vulnerable group, some consider this description to be condescending, as it implies that all individuals who are economically disadvantaged are less able to protect their own interests than others.⁹ Additionally, members of certain population subgroups might be vulnerable in some circumstances but not in others; for example, a pregnant woman might be vulnerable during active labor, but not at other points of her pregnancy.¹⁰ A further limitation of the categorical definition of vulnerability is that it does not capture the extent to which individual research participants might be vulnerable in multiple ways, for example, a child who also is economically disadvantaged. This limitation can result in inadequate safeguards for research participants whose vulnerability stems from more than one characteristic.

2. Contextual Vulnerability

In its 2001 report, *Ethical and Policy Issues in Human Subjects Research*, the National Bioethics Advisory Commission (NBAC) proposed an alternative to the categorical definition of vulnerability, highlighting the extent to which vulnerability in research subjects is sensitive to context.¹¹ NBAC described six types of vulnerability that could apply to research participants in different circumstances:

1. Cognitive or communicative vulnerability: the inability to understand information and make decisions, either due to capacity (e.g., young children), or circumstances (e.g., a stressful emergency or language barrier).
2. Institutional vulnerability: being subject to an authority relationship in a formal hierarchical structure (e.g., prisoners or military personnel).
3. Deferential vulnerability: being subject to the authority of others (e.g., children or military personnel).
4. Medical vulnerability: having a serious health condition for which there is no satisfactory standard treatment.

⁸ Silvers, A. (2004). Historical vulnerability and special scrutiny: Precautions against discrimination in medical research. *American Journal of Bioethics*, 4(3), 56-57.

⁹ Levine, C. (2008). Research Involving Economically Disadvantaged Participants. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 431-436). New York, NY: Oxford University Press.

¹⁰ Levine, C., et al. (2004). The limitations of ‘vulnerability’ as a protection for human research participants. *American Journal of Bioethics*, 4(3), 44-49; National Bioethics Advisory Commission (NBAC). (2001, August). *Ethical and Policy Issues in Research Involving Human Participants: Volume I*. Bethesda, MD: NBAC, p. 91.

¹¹ NBAC, (2001, August), op cit, p. 87.



5. Economic vulnerability: being disadvantaged in the distribution of social goods and services such as income, housing, or health care.
6. Social vulnerability: being a member of an undervalued or disenfranchised social group.

NBAC recommended that guidance for review of research be oriented around “how to identify and avoid situations that render some participants or groups vulnerable to harm or coercion” and argued that this approach, in which vulnerability is understood in terms of a person’s context, better expresses the ethical principle of respect for persons by treating people as individuals rather than solely as members of a group.¹² The contextual approach might be better suited than the categorical approach to situations in which research participants’ vulnerability stems not from an intrinsic inability to protect their own interests, but rather from aspects of their circumstances that might affect individuals differently and undermine one’s ability fully to exercise decision making capacity. A potential limitation of the contextual approach is that it requires a more nuanced assessment of individual circumstances that is not always feasible in the context of public policy, where it might be necessary to designate whole groups for special treatment (e.g., children, or persons who are permanently cognitively impaired).¹³

B. Examples of Potentially Vulnerable Populations

1. Children

Children are a vulnerable population because of their inability ethically and legally to consent to participate in research, and because of a perceived need to defer to adult authority, a lack of independent resources for autonomous decision making, and potential influence by “longstanding institutionalized relationships of adult authority and power.”¹⁴ Additional protections are required to ensure that children participating in research are not placed at unnecessary risk for the benefit of others. These additional safeguards are articulated in existing regulations and include seeking and obtaining parental permission, seeking and obtaining meaningful child assent or dissent when developmentally appropriate, and limiting the degree of allowable research-related risk.¹⁵

¹² Ibid, p. 92.

¹³ Levine, C., et al. (2004). The limitations of ‘vulnerability’ as a protection for human research participants. *American Journal of Bioethics*, 4(3), 44-49.

¹⁴ PCSBI, (2013, March), op cit, p. 26; Kipnis, K. (2003). Seven vulnerabilities in the pediatric research subject. *Theoretical Medicine*, 24, 107-120.

¹⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46 Subpart D: Additional Protections for Children Involved as Subjects in Research.



2. Decisionally Impaired Individuals

Decisionally or cognitively impaired individuals are potentially vulnerable because of limited capacity to give informed consent to participate in research. Informed consent is the process of informing and obtaining permission from an individual before conducting medical or research procedures or tests. In the research setting, this involves researchers educating prospective research participants about the risks and potential benefits of a proposed study and prospectively seeking their consent to participate. Seeking and

The Willowbrook Hepatitis Study

In the Willowbrook Hepatitis Study, researchers sought to understand the natural history of hepatitis and the effects of gamma globulin in conferring immunity and preventing the spread of hepatitis. Between 1956 and 1971, researchers deliberately infected children with hepatitis at the Willowbrook State School for mentally impaired children in Staten Island, New York. Hepatitis was endemic at Willowbrook, and researchers hoped the gamma globulin intervention would bring the disease under control and protect participants against future infection. Available records show that only those children whose parents gave permission participated in the study. The Willowbrook study has been held up as an example of the most serious breaches of research ethics. Critics of the study argue that the infection of healthy children at the school amounted to exploitation of an institutionalized and vulnerable population. They have challenged whether there was any benefit to the children from participating in the study; whether the researchers were justified in assuming that most participants, if not enrolled in the study, would have contracted the disease anyway given its prevalence at the school; and whether some parents were coerced into enrolling their children in the study because new admissions were possible only in Willowbrook's hepatitis research building, due to space limitations. Defenders of the study maintain that it was justified by its goal of controlling hepatitis at the school and providing long-lasting immunity to the children who participated.

Sources: Robinson, W.M. and B.T. Unruh (2008). The hepatitis experiments at the Willowbrook State School. In Emanuel, E.J., et al. (Eds.). (2008). *Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; Krugman, S. (1986). The Willowbrook hepatitis studies revisited: Ethical aspects. *Reviews of Infectious Diseases*, 8(1), 157-162; Beecher, H.K. (1966). Ethics and clinical research. *New England Journal of Medicine*, 274, 1354-1360; Goldby, S. (1971). Experiments at the Willowbrook State School. *Lancet*, 1(7702), 749; Goldman, L. (1973). The Willowbrook debate concluded? *World Medicine*, 9(2), 79-90.

obtaining informed consent is an integral part of the ethical treatment of individuals in both clinical and research settings. Individuals with impaired decision making capacity might be unable to fully understand the informed consent process or the implications of



participating in research, and as a result, their agreement to participate might not be considered ethically or legally valid.¹⁶

Decision making capacity is a complex skill set, and includes the abilities to make and express a choice, understand information relevant to a medical decision, appreciate the significance of this information for the individual's own situation, and reason with the relevant information in weighing options. For participants in research, decision making capacity also includes the ability to appreciate the differences between clinical care and research interventions.¹⁷

Decisional or cognitive impairment can stem from a number of causes, including some forms of mental illness, dementia, addiction, or mental disability, although individuals should not be presumed to lack decision making capacity simply in virtue of a diagnosis of a medical condition. Decision making capacity varies along a continuum, and individuals with some impairment might retain the ability to make certain types of decisions but not others. However, when potential research participants are likely to have impaired decision making capacity, they are appropriately considered vulnerable and in need of additional protections beyond those applicable to all research participants.¹⁸

Decisionally impaired individuals comprise an important group to consider in terms of vulnerability, both because of numerous historical cases of exploitation of this group in research, and because of an ongoing debate over when appropriate additional safeguards and regulatory protections should be in place.¹⁹

Current U.S. regulations include “mentally disabled persons” as a vulnerable group for whom additional safeguards should be provided.²⁰ The regulations also state that research with individuals who are unable to provide informed consent can proceed only with permission from a legally authorized representative (LAR), although the determination of who can serve as a LAR varies by state.²¹ However, the regulations do not provide a definition of what constitutes a mental disability, nor do they specify what additional

¹⁶ See the *Informed Consent: Background* module for further discussion of informed consent in human subjects research.

¹⁷ Rosenstein, D.L., and F.G. Miller. (2008). Research involving those at risk for impaired decision-making capacity. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 437-445). New York, NY: Oxford University Press.

¹⁸ Rosenstein, D.L., and F.G. Miller. (2008). Research involving those at risk for impaired decision-making capacity. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 437-445). New York, NY: Oxford University Press.

¹⁹ Moreno, J.D. (1998). Regulation of research on the decisionally impaired: History and gaps in the current regulatory system. *Journal of Health Care Law and Policy*, 1(1), 1-21.

²⁰ *Protection of Human Subjects*, HHS. 45 C.F.R. §46.111(b).

²¹ *Protection of Human Subjects*, HHS. 45 C.F.R. §46.111 and 46.116.



safeguards, beyond consent from an LAR, should be required for this group. Previous attempts at recommending additions to the regulations have met with resistance from scientists concerned that additional regulations would impede valuable research, and from those concerned about the adequacy of regulations to protect the dignity and well-being of research participants.²²

Scholars have suggested various ways in which protection for decisionally impaired research participants might be strengthened. Some recommend regulations similar to those for children in research; others suggest safeguards such as assessments of decision making capacity by someone independent of the research team, or inclusion in IRBs of members who are familiar with conditions that cause decisional impairment and the concerns of the population being studied.²³

3. Prisoners

Prisoners are vulnerable because physical isolation, lack of independence, and power differentials within command structures place them at greater risk of being manipulated or coerced into research.²⁴ The circumstances in which prisoners live limit their autonomy and capacity to exercise free choice, and therefore undermine their capacity to give voluntary informed consent to participate in research. For example, prisoners might feel that they have no choice but to participate in research, fearing punishment or denial of basic services. Additionally, their limited means might make them more willing to take on risk in exchange for special favors or treatment (e.g., more free time or easier work assignments). However, prisoners might choose freely to volunteer for research for a number of reasons. For example, some prisoners have expressed a desire to participate to make amends for their crimes, and others have reported that participation increased their self-esteem. Regulations for the inclusion of prisoners in research therefore attempt to reconcile the need to protect prisoners from exploitation and the need to allow them to choose freely the uses to which their bodies will be put.²⁵

²² Bonnie, R.J. (1997). Research with cognitively impaired subjects: Unfinished business in the regulation of human research. *Archives of General Psychiatry*, 54(2), 105-111.

²³ Rosenstein, D.L., and F.G. Miller. (2008). Research involving those at risk for impaired decision-making capacity. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 437-445). New York, NY: Oxford University Press; National Bioethics Advisory Commission (NBAC). (1998, December). *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. Volume I: Report and Recommendations of the National Bioethics Advisory Commission*. Bethesda, MD: NBAC.

²⁴ Bonham, V.H., and J.D. Moreno. (2008). Research with captive populations: Prisoners, Students, and Soldiers. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 461-474). New York, NY: Oxford University Press.

²⁵ *Ibid.*



4. Military Personnel

Military personnel also might feel pressure to participate in research because of the structured hierarchy in which they live and work. They might feel that participation could contribute to promotions, easier assignments, or special privileges; or that refusal to participate could result in demotions or other punitive measures. Moreover, the success of military operations depends in part on giving up some individual autonomy for the good of the whole; for this reason, soldiers might be coerced to participate in research if it is considered to be for the greater good; for example, accepting an experimental vaccine to ensure that the entire force would be protected.²⁶

Chemical Experiments in the Military

In 1942 military personnel began to be recruited for a series of chemical experiments conducted by the Chemical Warfare Service (CWS), part of the U.S. Army since 1918. Many of the tests involved exposure to mustard gas. Investigators wanted to obtain data on exposure levels that produce injuries, and to test protective clothing. Exposure to mustard gas can cause vomiting, eye swelling, blindness, internal and external bleeding, and severe skin blistering. The CWS used approximately 60,000 service personnel as subjects in these tests, some of whom died in the course of the experiments, and many of whom went on to develop long-term health problems. The test subjects were sworn to secrecy, and a 1993 report on the experiments by the National Academy of Sciences concluded that “[a]lthough the human subjects were called ‘volunteers,’ it was clear from the official reports that recruitment...was accomplished through lies and half-truths.” Reports from the time of the experiments describe how the cooperation of soldiers reluctant to participate could be secured by means of “a slight verbal ‘dressing down,’” and some field tests were conducted such that “declining to participate was not an option.”

Sources: Moreno, J.D. (2000). *Undue Risk: Secret State Experiments on Humans*. New York, NY: W.H. Freeman and Company; Bonham, V.H., and J.D. Moreno. (2008). Research with Captive Populations: Prisoners, Students, and Soldiers. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 461-474). New York, NY: Oxford University Press, p. 470; Pechurd, C.M., and D.P. Rall. (Eds.). Committee on the Survey of the Health Effects of Mustard Gas and Lewisite, Division of Health Promotion and Disease Prevention, Institute of Medicine. (1993). *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite*. Washington, DC: National Academy Press.

Existing legal standards provide protection to military personnel. Congress passed a law in 1998 prohibiting the administration of experimental drugs and drugs unapproved for their intended use to service members without their informed consent, although an exception to this policy is possible through a presidential waiver.²⁷

²⁶ Ibid.

²⁷ Ibid.



5. Participants in International Research

Concerns about exploitation of vulnerable populations are often raised in multinational research in which the investigators or sponsors are from a powerful industrialized country and the research is conducted in a low or middle income country.²⁸ Poverty, lack of access to health care, and disparities of power are just some of the reasons why members of populations in these countries might be considered vulnerable to exploitation in research, especially if the benefits of the research are unlikely to be available to the participants after the research is completed.²⁹ In addition, research participants in low or middle income countries might be vulnerable to an increased risk of harm from research if the country lacks the infrastructure, personnel, or oversight mechanisms to conduct the research safely.³⁰ These populations are at greater risk of being exploited or taken unfair advantage of in research, because they might be more willing to participate for unfair levels of benefit, exposed to higher risk due to lack of research infrastructure, or more likely to be enrolled in research that might result in benefits (e.g., new pharmaceuticals) to which they will not have access.³¹

The International Research Panel—a subcommittee of international experts in bioethics and biomedical research convened by the Bioethics Commission—addressed international research in resource-poor areas in its 2011 proceedings, *Research Across Borders*. It noted:

Populations in resource-poor areas might be willing to take on disproportionate risk and might be unable to provide informed consent. Informed consent alone, even among those with capacity to consent, is not sufficient to protect subjects. All of these factors demand due diligence and careful consideration.³²

One proposed strategy for minimizing potential exploitation when research is conducted in low or middle income countries is to ensure that the proposed study is responsive to the health needs and priorities of the local community and that the participants or their

²⁸ Macklin, R. (2003). Bioethics, vulnerability, and protection. *Bioethics*, 17(5-6), 472-486; Resnik, D.B. (2004). Research subjects in developing nations and vulnerability. *The American Journal of Bioethics*, 4(3), 63-64.

²⁹ Coleman, C.H. (2009). Vulnerability as a regulatory category in human subject research. *Journal of Law, Medicine & Ethics*, 37(1), 12-18.

³⁰ Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). (2012). *Ethical considerations in biomedical HIV prevention trials* [Additional guidance point added in 2012: UNAIDS/WHO guidance document. Geneva, Switzerland: UNAIDS.

³¹ Coleman, C.H., (2009), op cit; UNAIDS/WHO, (2012), op cit.

³² Presidential Commission for the Study of Bioethical Issues. (2011, September). *Research Across Borders: Proceedings of the International Research Panel of the Presidential Commission for the Study of Bioethical Issues*. Washington, DC: PCSBI, p. 19.



communities stand to benefit from the research. The *Declaration of Helsinki* and the Council for International Organizations of Medical Sciences' (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* both include such recommendations.³³ In addition, in its 2001 report, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, NBAC recommended that a developing country should only be selected as a research site when the proposed study responds to the host country's health needs.³⁴ In *Moral Science: Protecting Participants in Human Subjects Research*, the Bioethics Commission also recommended that ethical site selection for research take into consideration the responsiveness of the research to the needs of the community in which it is conducted. It acknowledged, however, that defining and implementing the criterion of responsiveness is a complex process, and that critical questions, such as who has the capacity and legitimate authority to define which research is adequately responsive to a community, and how best to prioritize the that community's health needs, remain in need of further examination.³⁵

C. Ethical Considerations in Research Involving Vulnerable Populations

A set of core ethical principles articulated in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* provide the foundation for the protection of human participants in research.³⁶ These principles include respect for persons, beneficence, and justice.

The principle of respect for persons recognizes persons as autonomous and capable of deliberating about their personal goals, considering their own choices and opinions, and determining their own lives. The *Belmont Report* establishes that all individuals engaging in research should be respected as autonomous decision makers or, if they are individuals with diminished autonomy, that they are entitled to additional protections.³⁷ The requirement of informed consent is a cornerstone of ethical research intended to enable persons to be treated respectfully and in accord with their understanding of their

³³ WMA Declaration of Helsinki, (2013), op cit; Council for International Organizations of Medical Sciences (CIOMS). (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: CIOMS.

³⁴ National Bioethics Advisory Commission (NBAC). (2001, April). *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*. Bethesda, MD: NBAC.

³⁵ Presidential Commission for the Study of Bioethical Issues. (2011, December). *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, p. 86.

³⁶ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare.

³⁷ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.



interests.³⁸ Since vulnerable individuals and groups might have a limited ability to protect their own interests through the process of informed consent, additional protections are critical to respecting their personhood. These protections can include parental permission and meaningful child assent (in the case of research with children), or the removal of inappropriate incentives or pressures to enroll (in the case of research involving prisoners or military personnel), among others.

The principle of beneficence, and its corollary non-maleficence, entails an obligation on the part of researchers to undertake efforts to maximize potential benefits and minimize potential harms to research participants.³⁹ Beneficence requires that special safeguards are employed to protect vulnerable populations, for example, placing strict limits on the level of risk acceptable in pediatric research.⁴⁰

The principle of justice is particularly salient in the context of vulnerable populations and subject selection for research more generally. Justice requires that we treat people equally, and calls for a fair distribution of the potential benefits and burdens of research.⁴¹ On an individual level, justice requires that research participants are selected fairly, for example, by mitigating as much as possible any bias in the referral process of patients to clinical trials.⁴² On the social level, justice requires that the burdens of research participation be distributed fairly across population subgroups, with those who are worse off, or more heavily burdened “by their infirmities and environments,” required to shoulder less of the burden of research participation.⁴³

Importantly, justice relates not only to the imposition of the burdens of research but also to the distribution of its benefits. The historical cases discussed in this module highlight the ways in which vulnerable populations have been unjustly exploited through their participation in research, but more recent history has also been concerned with injustices that result from excluding certain populations from research, or from failing to ensure access to the benefits of research. Concerns about the vulnerability of pregnant women and children, for example, have resulted in gaps in data on the safety and efficacy of

³⁸ PCSBI, (2011, September), *Ethically Impossible*, op cit, p. 95.

³⁹ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.

⁴⁰ PCSBI, (2013, March), op cit, p. 30.

⁴¹ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.

⁴² Meltzer, L.A., and J.F. Childress (2008). What is fair participant selection? In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 377-385). New York, NY: Oxford University Press.

⁴³ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.



medical interventions for these groups, with potentially dangerous implications.⁴⁴ During the HIV/AIDS epidemic, advocacy groups spearheaded attempts to extend access to experimental drug trials on the ground of ensuring fair access to the potential benefits of research.⁴⁵ Justice requires both protecting vulnerable populations from the burdens of research, and providing all individuals and groups with an equal opportunity to share in its benefits.⁴⁶

The core *Belmont Report* principles of respect for persons, beneficence, and justice are furthered by the principle of democratic deliberation, which the National Commission and subsequent commissions practiced in their work, and which the Bioethics Commission has explicitly added as a critical principle for publicly accountable decision making: “Democratic deliberation is a process that seeks to clarify and articulate factual and ethical issues at the core of a debate, to create consensus whenever possible, and to map the terrain of disagreements in a respectful way—when agreement is not immediately attainable—by encouraging reciprocity, respect for persons, transparency, publicity, and accountability.”⁴⁷ It provides a means to engage moral disagreement democratically, which promotes the legitimacy of collective decisions, encourages public-spirited perspectives, promotes mutually respectful decision making, and facilitates the correction of mistakes made while undertaking collective actions.⁴⁸

In research involving vulnerable populations, community engagement is particularly important as a component of a broader deliberation process. Including affected members of the community with whom the research will be conducted, or their guardians, advocates, or family members, in research-related decisions makes room for respectful discourse and encourages mutually respectful collective decision making. Engaging relevant communities in discussions about proposed research involving vulnerable groups can identify the potential for exploitation so that it can be prevented. For example, the National Commission’s 1977 report, *Research Involving Children*, recommended that research involving greater than minimal risk with no prospect of direct benefit to healthy children should be approved only after an opportunity for extensive public comment,

⁴⁴ Lyerly, A.D., Little, M.O., and R. Faden. (2008). The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics*, 1(2), 5-22; Macklin, R. (2010). Enrolling pregnant women in biomedical research. *Lancet*, 375, 632-633; Schonfeld, T. (2013). The perils of protection: Vulnerability and women in clinical research. *Theoretical Medicine and Bioethics*, 34, 189-206; PCSBI, (2013, March), op cit.

⁴⁵ Mastroianni, A., and J. Kahn. (2001). Swinging on the pendulum: Shifting views of justice in human subjects research. *Hastings Center Report*, 31(3), 21-28.

⁴⁶ Meltzer, L.A., and J.F. Childress, (2008), op cit.

⁴⁷ PCSBI, (2013, March), op cit, p. 34.

⁴⁸ Gutmann, A., and D. Thompson. (1997). Deliberating about bioethics. *Hastings Center Report*, 27(3), 38-41.



open deliberation, and national level review.⁴⁹ The Bioethics Commission echoed its commitment to democratic deliberation when it recommended that medical countermeasure research with pediatric participants include provision for community engagement.⁵⁰

To ensure that these ethical principles are followed, a careful and accountable independent ethics review of proposed research is generally required prior to the initiation of research and particularly in research with vulnerable populations. In the United States these reviews are conducted by IRBs, whose responsibilities are outlined in federal regulations.

D. Applicable Regulations and Guidelines

The history of contemporary regulations and guidelines for the protection of participants in human subjects research began with the Nuremberg Code, a legal and ethical code set forth in the final judgment by U.S. judges at the trial of Nazi doctors at Nuremberg in 1947.⁵¹ The Nuremberg Code includes many of what are now considered to be the basic principles governing the ethical conduct of research involving human participants, such as voluntary informed consent.

The revelation of controversial studies in the United States, such as the syphilis studies in Tuskegee and the Willowbrook study, led many to the conclusion that the virtue of individual researchers could not be relied upon to ensure adequate protection of research participants. On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), which described the basic ethical principles for the conduct of biomedical and behavioral research involving human participants in the *Belmont Report*, which was intended to serve as a guide for ethical human subjects research.⁵²

In the United States federal regulations govern research with human participants. These regulations are referred to as the Common Rule, and were codified by the U.S. Department of Health and Human Services in 1991 as 45 C.F.R. Part 46, Subpart A.⁵³

⁴⁹ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1977). *Research Involving Children* (DHEW Publication OS 77-0004). Washington, DC: Department of Health, Education, and Welfare.

⁵⁰ PCSBI, (2013, March), op cit.

⁵¹ Annas, G.J., and M.A. Grodin (2008). The Nuremberg Code. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 136-140). New York, NY: Oxford University Press.

⁵² The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.

⁵³ *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46, Subpart A. In addition to the Common Rule, the U.S. Food and Drug Administration (FDA), has codified its policies for the Protection of Human Subjects,



Eighteen federal agencies have adopted the Common Rule. The Common Rule applies to all research involving human participants supported or conducted by participating federal departments or agencies. It contains procedural requirements (e.g., independent review by an IRB and ongoing review requirements), as well as substantive requirements (e.g., requirements for informed consent, and criteria for IRB composition and approval).

Further subparts of the regulations detail additional safeguards required for research with specific vulnerable populations. In general, these Subparts set standards above and beyond those established in the Common Rule.

Subpart B, most recently revised in 2001, provides additional protections for pregnant women, human fetuses, and neonates involved in research.⁵⁴ This subpart was added to the regulations to encourage ethical research with pregnant women and neonates, populations that had been excluded from much research out of concern for the safety of both groups.

Subpart C provides additional protections relating to research involving prisoners as participants.⁵⁵ These regulations state that research involving prisoners is permissible only if it is minimal risk, will improve the health or wellbeing of the participant, and is a study directly relating to prisoners or prisons (e.g., research on a condition affecting prisoners as a class). If the research does not meet these conditions, it must be reviewed and approved by the Secretary of the U.S. Department of Health and Human Services (HHS) after consultation with appropriate experts. The regulations also require that IRBs reviewing research with prisoners include at least one member who is a prisoner or prisoner representative.

Subpart D provides additional protections for children participating in research.⁵⁶ These regulations require parental permission and child assent because children cannot legally or ethically give informed consent to participate in research. Only certain categories of research with children are permissible. Most permissible research involves minimal risk or offers the prospect of direct benefit to individual participants. Additional conditions apply to certain research activities involving children who are wards of the state or any other agency, institution, or entity.

at 21 C.F.R. Parts 50 and 56, which regulate research involving human subjects in the clinical trials of the products the agency regulates. See *Protection of Human Subjects*. 21 C.F.R. Part 50; and *Institutional Review Boards*. 21 C.F.R. Part 56.

⁵⁴ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.201-46.207.

⁵⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.301-46.306.

⁵⁶ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.401-46.409.



International guidelines, such as the World Medical Association’s *Declaration of Helsinki* and the CIOMS guidelines, recommend that special consideration be given to vulnerable populations in research.

E. Definitions of and Protections for Vulnerable Groups in Regulations, Codes, and Guidelines

The following table identifies the definitions of vulnerability and protections for vulnerable groups in key regulations, codes, and guidelines for the protection of human research participants.

Regulations or Guidelines	Definition of Vulnerability	Protections for Vulnerable Groups
United States		
<i>U.S. Code of Federal Regulations: Protection of Human Subjects, HHS, 45 C.F.R. § 46.111(b)</i> ⁵⁷		
	<p>Definition: Likely to be vulnerable to coercion or undue influence.</p> <p>Identified Vulnerable Groups: Children, prisoners, pregnant women, mentally disabled persons, economically or educationally disadvantaged persons.</p>	<p>IRBs must ensure that “additional safeguards” are included in the study to “protect the rights and welfare of these subjects.”</p> <p>Additional protections are specified for:</p> <ul style="list-style-type: none"> • Pregnant women, fetuses, and neonates (45 C.F.R. § 46 Subpart B) • Prisoners (45 C.F.R. § 46 Subpart C) • Children (45 C.F.R. § 46 Subpart D)
<i>The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1978)</i> ⁵⁸		
	<p>Definition: Dependent status, compromised capacity for informed consent, manipulability due to illness or socioeconomic condition.</p> <p>Identified Vulnerable Groups: Racial minorities, the economically disadvantaged, the very sick, and the institutionalized.</p>	<p>Researchers should:</p> <ul style="list-style-type: none"> • Select those less burdened by “their infirmities and environments” to accept risks of research. • Recruit only participants from groups likely to benefit from research.
Multinational		
<i>Council for International Organizations of the Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)</i> ⁵⁹		
	<p>Definition: Vulnerable persons have “insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.”</p> <p>Identified Vulnerable Groups: Children, persons with mental or behavioral disorders, junior or subordinate members of a hierarchical</p>	<p>Research with a vulnerable group is justified if:</p> <ul style="list-style-type: none"> • Research cannot be carried out equally well with less vulnerable subjects. • Research is responsive to health needs of the group. • Participants and other members of the

⁵⁷ *Protection of Human Subjects, HHS, 45 C.F.R. § 46.111(b).*

⁵⁸ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, (1978), op cit.

⁵⁹ CIOMS, (2002), op cit.



	<p>group, the elderly, residents of nursing homes, people receiving welfare benefits, the poor, the unemployed, patients in emergency rooms, some ethnic and minority groups, homeless persons, nomads, refugees or displaced persons, prisoners, patients with incurable disease, the politically powerless, members of communities unfamiliar with modern medical concepts, persons with serious, potentially disabling, or life-threatening diseases.</p>	<p>group will have reasonable access to the benefits of the research (e.g., diagnostic, preventive or therapeutic products).</p> <ul style="list-style-type: none"> • There are limitations on risk. • Permission from legal guardians or other appropriate representatives is obtained.
<p><i>International Conference on Harmonisation (ICH): Guideline for Good Clinical Practice (1996)</i>⁶⁰</p>		
	<p>Definition: “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.”</p> <p>Identified Vulnerable Groups: Members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students; subordinate hospital and laboratory personnel; employees of the pharmaceutical industry; members of the armed forces; persons kept in detention; patients with incurable diseases; persons in nursing homes; unemployed or impoverished persons; patients in emergency situations; ethnic minority groups; homeless persons; nomads; refugees; minors; and those incapable of giving consent.</p>	<p>Research should include:</p> <ul style="list-style-type: none"> • Oversight by an IRB/IEC to safeguard the rights, safety, and wellbeing of all trial subjects. • Special attention for trials that may include vulnerable subjects.
<p>Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO): <i>Ethical Considerations in Biomedical HIV Prevention Trials</i> (2012)⁶¹</p>		
	<p>Definition: Determinants of vulnerability include: poverty, age, gender, ethnicity, sexuality, health, employment, education, and legal conditions.</p> <p>Identified Vulnerable Groups: Women, children and adolescents, men who have sex with men, injecting drug users, sex workers, transgender persons, indigenous populations, the poor, the homeless, and communities from resource-poor settings.</p>	<p>Researchers should:</p> <ul style="list-style-type: none"> • Conduct social and political analysis to assess determinants of vulnerability in the community. • Conduct ongoing monitoring of the impact of a trial on the vulnerabilities of participating communities. • Provide assurance of confidentiality, freedom to decline to participate, right to withdraw at any time without penalty.

⁶⁰ International Conference on Harmonisation (ICH). (1996). *Guideline for Good Clinical Practice E6(R1)*. Retrieved August 13, 2014 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

⁶¹ UNAIDS/WHO, (2012), op cit.



World Health Organization (WHO): <i>Handbook for Good Clinical Research Practice</i> (2002) ⁶²		
	<p>Definition: Adopts CIOMS definition. Additionally states that “all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable.”</p> <p>Identified Vulnerable Groups: Children, individuals with diminished mental capacity, prisoners, institutionalized persons (including orphans), patients in emergency situations, the economically disadvantaged, individuals who cannot give consent.</p>	<p>Safeguards include, but are not limited to the following actions:</p> <ul style="list-style-type: none"> • Provide special justification that the research could not be carried out equally well with less vulnerable subjects. • Seek permission of a legal guardian or other legally authorized representative when the prospective participant is otherwise substantially unable to give informed consent. • Include an impartial witness to attend the informed consent process if the participant or the participant’s legally authorized representative cannot read. • Arrange for additional monitoring of the conduct of the study.
World Medical Association: <i>Declaration of Helsinki</i> (1964, revised 2013) ⁶³		
	<p>Definition: An increased likelihood of being wronged or of incurring additional harm.</p> <p>Identified Vulnerable Groups: Unspecified.</p>	<p>Research with a vulnerable group is only justified if:</p> <ul style="list-style-type: none"> • “Research is responsive to the health needs or priorities of this group” and cannot be carried out in a non-vulnerable group. • The group stands to “benefit from the knowledge, practices or interventions that result from the research.”

F. Timeline of Events that Shaped U.S. Human Subjects Research Ethics

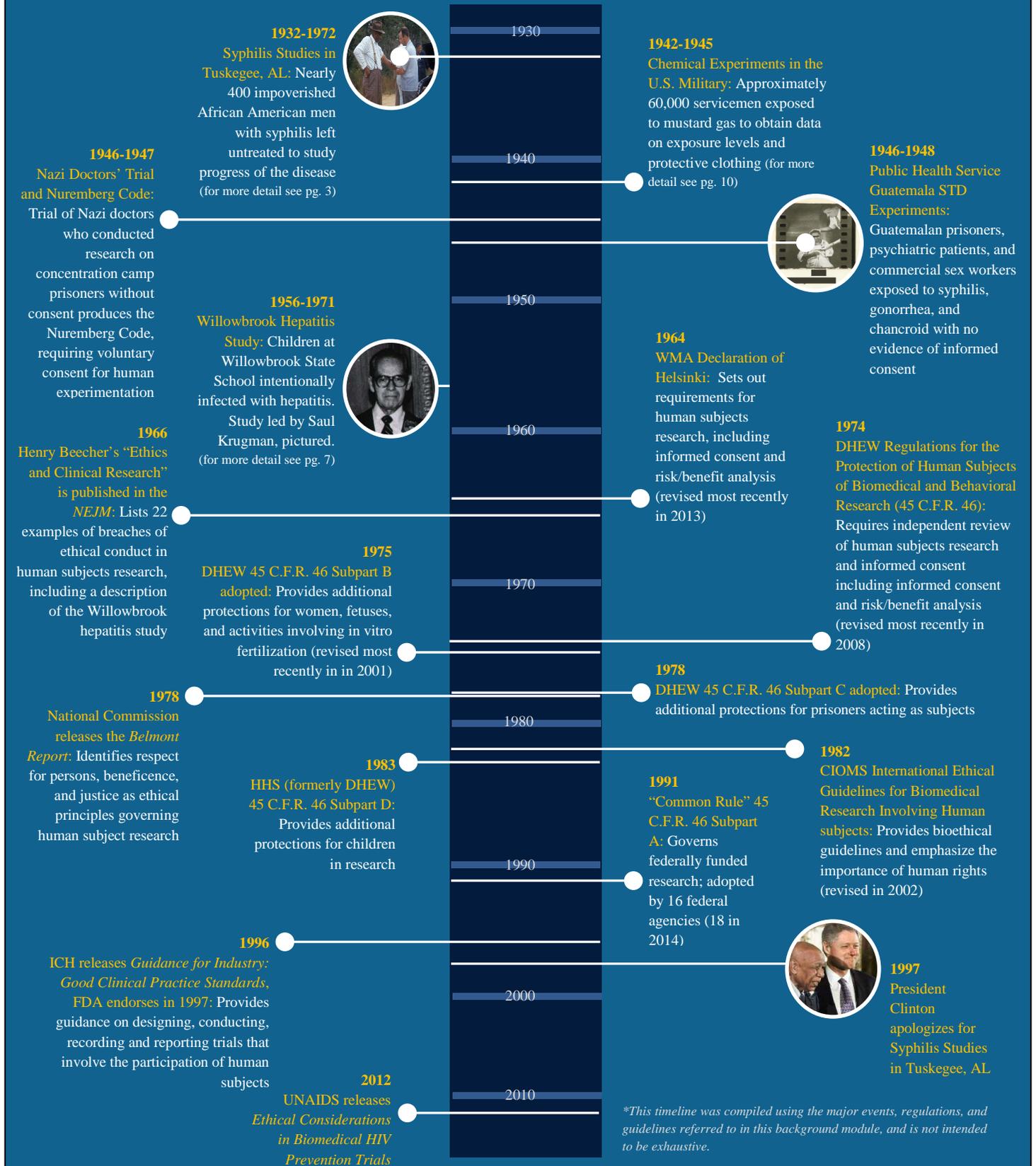
The following timeline highlights some historical landmarks in human subjects research with vulnerable populations that are discussed in this module, including legislation, regulations, and guidelines; and some of the historical cases that informed their development. In some instances agency names have changed (e.g., the Department of Health, Education, and Welfare (DHEW) is now HHS).

⁶² World Health Organization (WHO). (2002). *Handbook for Good Clinical Research Practice (GCP)*. Retrieved August 13, 2014 from http://apps.who.int/prequal/info_general/documents/gcp/gcp1.pdf.

⁶³ WMA Declaration of Helsinki, (2013), op cit.



Timeline of Events that Shaped U.S. Human Subjects Research Ethics*



*This timeline was compiled using the major events, regulations, and guidelines referred to in this background module, and is not intended to be exhaustive.



V. Discussion Questions

The following questions are based on the information provided in the “Background” section above and are intended to reinforce important aspects of research with vulnerable populations. Important points are noted with each question to help the instructor guide a group discussion. The “Additional Resources” section will be helpful in answering these questions.

1. **When is the categorical (or subgroup) approach to defining vulnerability most applicable? How does the contextual approach help to resolve some of the limitations of the categorical approach?**

Starting points for discussion:

- a. The categorical approach is most applicable when the members of a group share an intrinsic characteristic that makes them vulnerable, such as immaturity in the case of children.
- b. The contextual approach is able to capture when individuals’ vulnerability stems from their circumstances, rather than from membership in a group or an intrinsic inability to protect their own interests.
- c. The contextual approach can capture when a person’s vulnerability stems from multiple sources.

2. **Why is it important that additional safeguards are in place to protect vulnerable individuals who participate in research?**

Starting points for discussion:

- a. Vulnerable individuals are at higher risk for being harmed or wronged in the research setting.
- b. Vulnerable individuals might be unfairly taken advantage of in the research setting.

3. **Vulnerability can depend on a person’s context, and someone might be vulnerable in one circumstance but not in another. For example, a pregnant woman might be vulnerable during active labor but not at other stages of her pregnancy. What factors should be considered in determining whether an individual or group of individuals is vulnerable?**



Starting points for discussion:

- a. Potential research participants are vulnerable if they are unable to give voluntary informed consent. The principle of respect for persons requires that research participants give informed, voluntary consent to participate, or its moral equivalent.
 - b. A person's capacity for voluntary informed consent might be compromised by their situation; for example, military personnel might fear that declining to participate in research will have negative implications for their careers.
 - c. A person's social and economic circumstances might make her vulnerable to exploitation if the research does not offer fair benefits or exposes her to high levels of risk.
- 4. Historical cases of research abuses are particularly ethically troubling from the point of view of vulnerable populations. Identify some current protections for vulnerable groups in research that have their origins in the reaction to these cases. How do these regulations help to protect vulnerable populations?**

Starting points for discussion:

- a. The *Nuremberg Code* articulated the central ethical requirement of obtaining voluntary informed consent from research participants, a cornerstone of contemporary regulations and guidelines for ethical human subjects research.
- b. The *Belmont Report* articulates core ethical principles for human subjects research (i.e., respect for persons, beneficence, and justice) that were often absent in the historical cases of research abuses.
- c. U.S. regulations governing human subjects research, adopted by 18 federal agencies, include special protections for vulnerable groups including children and prisoners that specify how consent must be obtained and the acceptable levels of risk for research with these groups.
- d. International regulations such as the *Declaration of Helsinki*, the CIOMS guidelines, and the UNAIDS guidelines highlight the need to develop carefully tailored protections for vulnerable groups in international research, as well as the need to include in research those who are most likely to benefit.



VI. Exercises

Exercise A. *On May 16, 1997, President Clinton officially apologized on behalf of the U.S. government to the survivors of the syphilis studies in Tuskegee and their families for the wrongs committed in the study. You can read the official transcript of the apology here:*

Remarks by the President in Apology for Study Done in Tuskegee. (1997).

Retrieved August 13, 2014 from

<http://clinton4.nara.gov/New/Remarks/Fri/19970516-898.html>.

- 1. In his apology, to which ethical principles and values did President Clinton appeal?**
- 2. Some scholars contend that the syphilis studies in Tuskegee might have had a lasting impact on how African Americans regard biomedical research, although distrust of medical and public health institutions can be traced back further, to the experiences of many African Americans as victims of medical experiments during slavery.⁶⁴ Are President Clinton's proposals for increasing trust in biomedical research appropriate and reasonable? Can you think of other actions that could be taken to engender trust?**
 - a. Engaging communities in the planning of proposed research can engender trust. See the Bioethics Commission's Community Engagement Background module for an overview on community engagement (available at <http://bioethics.gov/node/2870>). Discuss how engagement with the local community might have altered the design of the study, or prevented the study from proceeding.
 - b. Conduct a literature search for surveys or analysis of perceptions about or attitudes towards biomedical research among African Americans. Students might consider how the research community can work to regain trust and ensure that African Americans benefit from biomedical research.

Exercise B. *Read the following description of the Willowbrook Hepatitis Study:*

National Institutes of Health Clinical Center, Department of Bioethics. (2009).

Exploring Bioethics, Willowbrook Hepatitis Experiments. NIH Curriculum Supplement Series, Grades 9-12. Newton, MA: Educational Development Center, Inc. Retrieved August 13, 2014 from

⁶⁴ Gamble, V.N. (1997). Under the shadow of Tuskegee: African Americans and health care. *American Journal of Public Health*, 87(11), 1773-1778.



http://science.education.nih.gov/supplements/nih9/bioethics/guide/pdf/Master_5-4.pdf.

1. Do you think Dr. Krugman had a valid scientific justification for conducting this research?

- a. Was the possibility of naturally occurring infection in this population sufficient justification to conduct the research?
- b. Could the study have been conducted ethically in the adult population of Willowbrook employees? Would research with employees raise concerns about vulnerability as well?
- c. Why do you think the Willowbrook facility was chosen for the research? What additional concerns are raised due to the fact that the children at Willowbrook had mental disabilities?
- d. Is it ever appropriate to use a vulnerable, institutionalized population for research? Why or why not? What protections should be included?

2. If you were writing the letter seeking parental permission for children at Willowbrook to participate in research, what additional information would you include? Why?

The following additional readings might be helpful in answering this question:

Requirements for Permission by Parents or Guardians and for Assent by Children. 45 C.F.R. § 46.408.

American Academy of Pediatrics. (1995). Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*, 95(2), 314-317. Retrieved August 13, 2014 <http://pediatrics.aappublications.org/content/95/2/314.full.pdf+html>.

3. Might parents have been unduly influenced to provide their consent for this study?

- a. Search for the meaning of the term “undue influence” as it is used in legal and ethical contexts. Does it apply in this example?
- b. What actions or policies could have been taken to ensure that parents of children in the study provided permission based on the best interests of their child?

Exercise C: Watch the video “Manufacturing Madness” about experiments conducted by the United States Army testing chemical weapons at Edgewood Arsenal, a military facility located on the Chesapeake Bay. The experiments began before the Second World War, focusing on



mustard gas. After the war, the research shifted to testing nerve agents and psychochemicals. Subjects were soldiers who often did not know that they were being given these psychedelic agents, some of whom experienced lasting physical and mental health problems.

The video is available at:

Khatchadourian, R. (2012, December). Manufacturing madness. *The New Yorker*. Retrieved August 13, 2014 from <http://www.newyorker.com/online/blogs/newsdesk/2012/12/video-manufacturing-madness.html>.

- 1. Why might the soldiers involved in these studies be considered a vulnerable population?**
 - a. Discuss whether these subjects could be considered volunteers for research participation. What factors might have influenced their decisions to participate?
 - b. Note that the interviewers in the film are either wearing a white laboratory coat or a uniform. How might this influence subjects' perceptions of the activity in which they are engaged?
- 2. Were the soldiers who participated in these studies being exploited?**
 - a. Review the resources linked to this video that describe how these experiments were used for military propaganda films.
 - b. Discuss the relevance of subjects' awareness, or lack of awareness, that they were being filmed during the experiments.
 - c. What were the goals of this research and who stood to benefit from it?

VII. Glossary of Terms

Autonomy: The capacity to direct the course of one's own life or to live according to one's own values and beliefs.

Beneficence: The ethical principle that calls upon health care providers and researchers to promote the interests and wellbeing of patients and participants.



Common Rule: U.S. federal regulations that protect research participants, codified by the U.S. Department of Health and Human Services in the Code of Federal Regulations at 45 C.F.R. Part 46, Subpart A. Also known as “Human Subjects Regulations.”

Community-engaged research: A mechanism to involve members of a community in the planning and execution of research, including individuals who will be affected by or who are in a position to influence the course of research.

Community engagement: The process of working collaboratively and engaging actively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the wellbeing of those people. [Adapted from *Principles of Community Engagement*, Second Edition (2011)].

Democratic deliberation: A method of decision making to address an open policy question in which participants consider both relevant information and ethical aspects, justify their arguments with reasons, and treat one another with mutual respect, with the goal of reaching an actionable decision for policy or law, open to future challenge or revision.

Distributive justice: The ethical principle that calls for equitable distribution of benefits and burdens across society—for example, the benefits and burdens of biomedical research, or of technological advances.

Exploitation: In human subjects research, taking unfair advantage of participant vulnerability.

Informed consent: The process of informing and obtaining permission from an individual before conducting medical or research procedures or tests.

Institutional review board (IRB): A specially constituted review body established or designated by an entity to safeguard the rights and welfare of human research participants. The duties and responsibilities of IRBs are described in U.S. federal regulations.

Respect for persons: The ethical principle that calls on health professionals and researchers to treat individuals as independent and self-determining (autonomous) agents and to provide additional protections to persons with diminished autonomy in clinical care and research settings.

Vulnerable populations: Groups of individuals who are potentially unable to exercise control over how their interests are represented and pursued.



VIII. Additional Resources

American Academy of Pediatrics. (1995). Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*, 95(2), 314-317.

Annas, G.J., and M.A. Grodin. (2008). The Nuremberg Code. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 136-140). New York, NY: Oxford University Press.

Ashcroft, R.E. (2008). The Declaration of Helsinki. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 141-148). New York, NY: Oxford University Press.

Beauchamp, T.L. (2008). The Belmont Report. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 149-155). New York, NY: Oxford University Press.

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Bonnie, R.J. (1997). Research with cognitively impaired subjects: Unfinished business in the regulation of human research. *Archives of General Psychiatry*, 54(2), 105-111.

Bonham, V.H., and J.D. Moreno. (2008). Research with Captive Populations: Prisoners, Students, and Soldiers. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 461-474). New York, NY: Oxford University Press.

Brandt, A.M. (1978). Racism and research: The case of the Tuskegee Syphilis Study. *Hastings Center Report*, 8(6), 21-29.

Centers for Disease Control and Prevention (CDC). (n.d.). U.S. Public Health Service Syphilis Study at Tuskegee: The Tuskegee Timeline. Retrieved August 13, 2014 from <http://www.cdc.gov/tuskegee/timeline.htm>.

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Committee to Survey the Health Effects of Mustard Gas and Lewisite, Division of Health Promotion and Disease Prevention, Institute of Medicine. (1993). *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite*. Washington, DC: National Academy Press.

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