



Vulnerable Populations in *Gray Matters*

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I. Introduction

Human participation in research presents ethical challenges related to the dual goals of safeguarding the wellbeing of participants and promoting advances in scientific understanding. Research ethics addresses special consideration and steps to take when research participants include those who are vulnerable, or unable to exercise control over how their interests are represented and pursued. Some individuals or groups that participate in research are vulnerable in ways that put them at increased risk of being exploited or unfairly taken advantage of in the research setting.¹ Researchers must take care that they do not take unfair advantage of participants to spur scientific progress.

¹ See the *Vulnerable Populations Background* module for a further discussion of vulnerability in the research setting. The module is available at www.bioethics.gov/education.



Neuroscientists might undertake research involving a variety of vulnerable populations. Sources of vulnerability relevant in neuroscience might include: limits on capacity to decide about research participation, relationships of power or authority, pressures that socialize individuals to defer to the desires of others despite an inner reluctance, medical diagnoses that alter participants' risk-benefit calculations, and existing disparities in distribution of social burdens and benefits.² In its discussion of neuroscience, the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) addressed ethical issues particularly related to some sources of vulnerability.

Notably, some individuals that participate in research are vulnerable because they lack the capacity—or have an impaired capacity—to provide voluntary informed consent. Informed consent is a cornerstone of research ethics, and scientists, regulators, participants, and their caregivers must consider carefully how research can be conducted ethically when consent cannot be provided. Other potential participants who face devastating illness or injury might be vulnerable due to desperation and a lack of treatment options.

In addition, other research participants might be vulnerable because they live in circumstances that limit their capacity to exercise free choice, such as prisoners. These constraints can limit one's capacity to decide to participate in research. Prisoners might feel that research participation is not optional, fearing reprisal, or might be willing to take on greater risk given limited opportunities to acquire proffered benefits of participation (e.g., free time or an easier work assignment).

The Bioethics Commission produced a two-volume report on ethics and neuroscience, collectively called *Gray Matters*. In [*Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*](#) (*Gray Matters*, Vol. 1), the Bioethics Commission emphasized the importance of integrating ethics and neuroscience research early and explicitly throughout the research process.³ In [*Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society*](#) (*Gray Matters*, Vol. 2), the Bioethics Commission addressed three ethically controversial topics at the intersection of neuroscience and society: cognitive enhancement, consent capacity, and neuroscience and the legal system.

² Presidential Commission for the Study of Bioethical Issues (PCSBI). (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*, Appendix I: Sources of Pediatric Vulnerability. Washington, DC: PCSBI, p. 126.

³ Presidential Commission for the Study of Bioethical Issues (PCSBI). (2014, May). *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*. Washington, DC: PCSBI.



It sought to clarify the current state of the field, identify common ground, and facilitate productive discourse.⁴

Contemporary neuroscience research presents an opportunity to achieve a deeper understanding of brain-related disorders, and to address an important public health burden. Millions of individuals in the United States, and more than one billion individuals globally, suffer from neurological disorders.⁵ Most individuals will be affected by some form of neurological impairment, either as patients or as caregivers for affected loved ones. Neuroscientists who conduct research involving human participants commonly work with populations or individuals whose consent capacity might be absent, impaired, fluctuating, or in question. In addition, the concept of consent capacity, the causes of its impairment, and its potential to be restored through therapeutic intervention are areas that stand to benefit from the fruits of neuroscience research. Neuroscience research could help refine our understanding and assessment of decision-making capacity, including consent capacity, and its underlying neurological correlates.⁶

II. Learning Objectives

After completing this activity, students should be able to:

1. Describe the ways in which individuals with impaired consent capacity are a vulnerable population.
2. Understand circumstances that might make potential participants vulnerable, and merit ethical consideration in neuroscience.
3. Discuss additional protections researchers can employ to protect vulnerable participants, including those with impaired consent capacity.

III. Background

A. Consent Capacity and Vulnerable Populations

⁴ Presidential Commission for the Study of Bioethical Issues (PCSBI). (2015, March). *Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society*. Washington, DC: PCSBI.

⁵ National Institute of Neurological Disorders and Stroke (NINDS). (2014). NINDS Overview. Retrieved February 2, 2015 from http://www.ninds.nih.gov/about_ninds/ninds_overview.htm; BrainFacts.org. (2014). Global Burden of Neurological and Mental Disorders [Webpage]. Retrieved February 17, 2015 from <http://www.brainfacts.org/policymakers/global-burden-of-neurological-and-mental-disorders/>.

⁶ Palmer, B.W., and G.N. Savla. (2007). The association of specific neuropsychological deficits with capacity to consent to research or treatment. *Journal of the International Neuropsychological Society*, 13(6), 1047-1059.



Research participants who might have impaired consent capacity can be vulnerable in different ways. First, they might be inappropriately included in research, when researchers appear to obtain consent but these individuals, in fact, are unable to provide ethically or legally valid informed consent to participate. This error has moral consequences because it can lead to harm or exploitation of such participants for the social benefit of knowledge gained from neuroscience research. Second, those who have consent capacity might be inappropriately excluded from research participation as the result of mistaken assumptions about their decision-making abilities based on generalizations about a particular diagnosis. This error is disrespectful of the autonomy of those excluded, and can be considered unfair if it results from treating individuals differently without justification.

Over the last four decades, institutions and individuals have sought to achieve two goals in research involving individuals who might lack consent capacity: protecting participants against exploitation and refraining from unjustly or unnecessarily excluding potential participants who retain consent capacity. This dual mission—protection and inclusion to ensure the benefits of research are distributed equitably—shapes many core ethical considerations about protecting vulnerable participants in research.

The capacity to make decisions comprises abilities that are relevant to all choices that an individual might make. Because individuals make so many different kinds of choices, decision-making capacities are often thought to be task-specific, or different depending on the kind of decision being made. For example, consent capacity includes the ability to understand information relevant to a decision, appreciate the significance of this information for the individual's own situation, reason with the relevant information in weighing options, and make and express a choice.⁷ For research participants, consent capacity also includes the ability to appreciate the differences between clinical care and research interventions.⁸

Vulnerability is related to exploitation—individuals are vulnerable if they can be taken unfair advantage of more easily than others. Impaired consent capacity is often thought of as a distinct source of vulnerability given the ethical importance of informed and voluntary consent to research participation.⁹ Research participants' consent capacity also can depend on situational sources of vulnerability, including environmental and social

⁷ Appelbaum, P.S. (2010). Consent in impaired populations. *Current Neurology and Neuroscience Reports*, 10(5), 367-373.

⁸ 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.

⁹ PCSBI, (2013, March), *Safeguarding Children*, op cit., p. 126.



features of some contexts in which the research takes place. For example, recent research shows some individuals living with schizophrenia have consent capacity when informed consent processes are modified to accommodate differences in learning and memory.¹⁰ In addition, the history of individuals living with neurological disorders is inextricably linked to vulnerability related to institutionalization. Residing in institutions can render individuals a convenient subject pool, reflecting how the vulnerability of those with neurological disorders can be dependent on their circumstances.

Neuroscience research might involve individuals diagnosed with neurological disorders that can, but do not always, cause an inability to understand and autonomously choose to participate in research. These individuals might be considered members of a potentially vulnerable population if their consent capacity is unknown. Different individuals with the same diagnosed condition can exhibit varying capacities, depending on environment, relationships, severity of the condition, and neuropsychological functions. Social sources of vulnerability involve entrenched stereotypical thinking that compromises consideration due to members of a group whose rights and interests have been socially disvalued.¹¹ Equating certain conditions with impaired consent capacity or making unfounded assumptions about individual abilities based on diagnoses can reflect stereotypes that undermine the respect due to those individuals.

Labeling those with specific diagnoses as vulnerable can have unintended consequences. For example, it can reinforce gross generalizations that fail to capture and demonstrate respect for important individual differences within large and varied groups.¹² This is an important consideration in neuroscience research, given the wide variety of neurological impairments under investigation, and the diverse experiences of those living with impairments. Nevertheless, invoking the concept of vulnerability calls our attention to how research with some human participants warrants special scrutiny.¹³ Employing a vulnerable population framework serves a vital practical and ethical function in research practice and oversight. Recognizing the specific needs and considerations of a vulnerable population is an important step in putting appropriate research protections in place.

¹⁰ Jeste, D.V., et al. (2009). Multimedia consent for research in people with schizophrenia and normal subjects: A randomized trial. *Schizophrenia Bulletin*, 35(4), 719-729.

¹¹ PCSBI, (2013, March), *Safeguarding Children*, op cit., p. 126.

¹² Levine, C., et al. (2004). The limitations of “vulnerability” as a protection for human research participants. *American Journal of Bioethics*, 4(3), 44-49; Mental Health Foundation. (2012). Mental Capacity and the Mental Capacity Act 2005: A Literature Review. Retrieved February 3, 2015 from <http://www.mentalhealth.org.uk/content/assets/PDF/publications/mca-lit-review.pdf>.

¹³ Levine, C., et al., op cit.



B. Other Potential Vulnerabilities

Desperate Patients

Vulnerability related to impaired consent capacity can be inappropriately conflated with other constraints on decision making, such as desperation resulting from lack of treatment options.¹⁴ When research appears to offer patients hope, these high stakes can affect participant decision making. In the context of clinical neuroscience research, some patients who participate in research can be desperate to find an intervention that helps alleviate their suffering. Some experimental neurosurgical trials have raised concerns about desperation.¹⁵ Desperation is distinct from impaired consent capacity. It can affect individuals' decisions about research participation by altering their risk perception. Other evidence indicates that concerns about coercion, desperation, or participants' expectations that research participation confers medical benefit—referred to as the therapeutic misconception—are distinct from whether a person cannot consent because of impaired consent capacity.¹⁶ Concerns about desperation are not unique to neuroscience. Much clinical research involves new interventions for conditions with poor outcomes.¹⁷ More research is needed to better understand the different influences of vulnerability, desperation, and affective states on decision making.

Prisoners

Prisoners are considered vulnerable because physical isolation, lack of independence, and power dynamics can place them at greater risk of being manipulated or coerced into participating in research.¹⁸ 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 face different pressures to participate in research, fearing punishment or denial of basic services. In addition, special favors or treatment (e.g., useful objects or more free time)

¹⁴ Bell, E., et al. (2014). Beyond consent in research: Revisiting vulnerability in deep brain stimulation for psychiatric disorders. *Cambridge Quarterly of Healthcare Ethics*, 23(3), 361-368.

¹⁵ Ford, P.J. (2009). Vulnerable brains: Research ethics and neurosurgical patients. *Journal of Law, Medicine & Ethics*, 37(1), 73-82.

¹⁶ Fisher, C.E., et al. (2012). The ethics of research on deep brain stimulation for depression: Decisional capacity and therapeutic misconception. *Annals of the New York Academy of Sciences*, 1265, 69-79; Christopher, P.P., et al. (2012). Enrolling in deep brain stimulation for depression: Influences on potential subjects' decision making. *Depression and Anxiety*, 29(2), 139-146.

¹⁷ Casarett, D.J. and J.H.T. Karlawish. (2000). Are special ethical guidelines needed for palliative care research? *Journal of Pain and Symptom Management*, 20(2), 130-139.

¹⁸ 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.



can take on different value in a context where resources and rewards are scarce, leaving prisoners more willing to take on risks of participation.

Regulations for the inclusion of prisoners in research 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.¹⁹ Additional protective measures, such as including prisoner representatives on Institutional Review Boards (IRBs) that oversee research involving prisoners as participants, help ensure that prisoners are choosing freely to volunteer for research. Regulatory subparts, such as Subpart C for permitted research involving prisoners, often outline a process tailored to safeguard the interests of the specified vulnerable population.²⁰

Some neuroscience research results can inform legal proceedings, including criminal prosecution and sentencing. Prisoners are sometimes included in such neuroscience research, the findings of which are increasingly being used to inform legal policies and practices. For example, some research using functional magnetic resonance imaging (fMRI) scans to investigate the biological underpinnings of psychopathy has included prisoners as participants.²¹ Prisoners are included because rates of psychopathy are higher among criminals. In addition, such research is pertinent to social policy and prisoners more broadly, as other research findings indicate that prisoners with psychopathy are more likely to reoffend.²²

Neuroscience research also might help support better policies regarding incarceration. For example, research on solitary confinement reveals that it can cause psychological harm among individuals with no history of mental illness and can exacerbate preexisting disorders.²³ Neuroscientists include prisoners as participants in order to investigate which practices are successful at deterring future crime while simultaneously treating prisoners

¹⁹ Ibid.

²⁰ *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46, §46.306.

²¹ Aronson, J.D. (2010). The law's use of brain evidence. *Annual Review of Law and Social Science*, 6, 93-108; Snead, O.C. (2007). Neuroimaging and the "complexity" of capital punishment. *NYU Law Review*, 82, 1265-1339.

²² Rushing, S.E. (2012). The admissibility of brain scans in criminal trials: The case of positron emission tomography. *Court Review*, 50(2), 62-69; Edersheim, J.G., Brendel, R.W., and B.H. Price. (2012). Neuroimaging, Diminished Capacity and Mitigation. In J.R. Simpson. (Ed.). *Neuroimaging in Forensic Psychiatry: From the Clinic to the Courtroom*, First Edition (pp. 163-193). Chichester, UK: Wiley-Blackwell.

²³ Grassian, S. (2006). Psychiatric effects of solitary confinement. *Journal of Law & Policy*, 22, 325-383; Smith, P.S. (2006). The effects of solitary confinement on prison inmates: A brief history and review of the literature. *Crime and Justice*, 34(1), 441-528.



humanely. This kind of neuroscience research raises questions about how to appropriately and ethically include prisoners in such research, as well as questions about the implications that the research has for society and the law.

C. Additional Protections

A variety of research practices have been proposed to protect the interests of those with potentially impaired consent capacity. Proposed protections include initial and ongoing assessment of consent capacity; modified informed consent processes to accommodate participants’ needs, such as audiovisual means or paced verbal instructions; methods to respect assent and dissent when consent capacity is partial or in question; independent consent monitors; limits on risk; clear parameters and procedures for obtaining the permission of a legally authorized representative (LAR) when a participant lacks consent capacity; research advance directives; and stakeholder engagement. The following table provides a brief description and example of selected protections.

Selected Protections for Individuals with Potentially Impaired Consent Capacity	
Additional Protections	Description/Example
Consent Capacity Assessment	Tools or means for evaluating a potential research participants’ consent capacity in research Example: MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) ²⁴
Modified Procedures	Alterations to the informed consent process to accommodate individuals’ impairments Example: Multimedia presentation of information about a research protocol can improve potential participants’ comprehension among participants diagnosed with schizophrenia ²⁵
Methods to Respect Assent and Dissent	Seeking participants’ assent to participate and respecting dissent in addition to obtaining permission from a legally authorized representative (LAR) Example: Stakeholder-informed recommendations for assent and dissent in dementia research ²⁶
Independent Consent Monitors	Those external to or independent of a research protocol can help prevent coercion and guard against conflicts of interest Example: IRBs can require consent auditors to observe the consent process and determine whether participants consent, are incapable of consent but assent to participate, or dissent ²⁷

²⁴ Appelbaum, P.S., and T. Grisso. (2001). MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Sarasota, FL: Professional Resource Press.

²⁵ Jeste, D.V., et al. (2009). Multimedia consent for research in people with schizophrenia and normal subjects: A randomized trial. *Schizophrenia Bulletin*, 35(4), 719-729

²⁶ Black, B.S., et al. (2010). Seeking assent and respecting dissent in dementia research. *American Journal of Geriatric Psychiatry*, 18(1), 77-85.



Limits of Acceptable Levels of Risk	Placing an upper limit on the degree, likelihood, or kind of permissible risks in research. Example: IRBs can develop written policies and procedures that define and limit research risk ²⁸
Legally Authorized Representatives (LARs)	Surrogate or proxy decision makers with the legal standing to make decisions on behalf of others are required by regulation when participants cannot consent on their own behalf Example: LARs appointed for medical care can make certain research enrollment decisions under applicable state law ²⁹
Research Advance Directives	Individuals express preferences about future research participation in case their consent capacity becomes impaired. They can select categories of research in which they would be willing to participate; delineate values, goals, and limitations to guide their participation; and designate an LAR to make research decisions Example: NIH Clinical Center advance directives for both health care and medical research ³⁰
Stakeholder Engagement	Seeking out the perspectives of individuals and groups likely to be involved in research or affected by its results Example: Democratic deliberation by stakeholders about the ethics of LAR involvement in Alzheimer’s disease research ³¹

D. Regulations for Vulnerable Populations in Neuroscience

Federal regulations for the protection of human subjects in research are contained in Department of Health and Human Services (HHS) regulations at 45 Code of Federal Regulations (C.F.R.) Part 46 and FDA regulations at 21 C.F.R. Part 50, among others.³² Subpart A of 45 C.F.R. Part 46, referred to as the Common Rule, governs research with adult participants.³³ The Common Rule establishes federal requirements for all federally

²⁷ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (1978). *Research Involving Those Institutionalized as Mentally Infirm*. Washington, DC: Department of Health, Education, and Welfare. Retrieved April 16, 2015 from http://videocast.nih.gov/pdf/ohrp_research_mentally_infirm.pdf, pp. 11-16.

²⁸ Secretary’s Advisory Committee on Human Research Protections (SACHRP). (2009). *Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIDR)*, pp. 10-11. Retrieved March 24, 2015 from <http://www.hhs.gov/ohrp/sachrp/20090715letterattach.pdf>.

²⁹ OHRP. (2011, January 20). *Frequently Asked Questions*. Retrieved April 30, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>. “Most states have no law specifically addressing the issue of consent in the research context. In these states, law that addresses who is authorized to give consent on behalf of another person to specific medical procedures or generally to medical treatment may be relevant if the research involves those medical procedures or medical treatment.”

³⁰ NIH. (n.d.). *NIH Advance Directive for Health Care and Medical Research Participation*, NIH-200 (10-00).

³¹ DeVries, R. , et al. (2010). Assessing the quality of democratic deliberation: A case study of public deliberation on the ethics of surrogate consent research. *Social Science and Medicine*, 70(12), 1896-1903.

³² The language of the two sets of regulations is substantively identical. The Bioethics Commission refers only to HHS regulations in this module, although the discussion encompasses the provisions of Subpart D as codified by both HHS and FDA.

³³ Eighteen federal agencies and departments have also adopted the Common Rule. They are: (1) Department of Agriculture (USDA); (2) Department of Commerce (DOC); (3) Department of Defense



supported human subjects research. These regulations include provisions for review of human subjects research by IRBs. Current federal regulations require that IRBs possess the necessary professional competence to review research activities, either through IRB members with appropriate experience and expertise or invited consultants.³⁴ Protections for some vulnerable populations have been delineated in subparts of the regulations. Subpart B describes protections for pregnant women and fetuses; Subpart C describes protections for prisoners; and Subpart D describes protections for children.³⁵

However, no subpart of the regulations directly addresses research participation of adults with impaired consent capacity. The Common Rule requires voluntary informed consent from participants or permission from their legally authorized representatives (LARs).³⁶ It also stipulates that researchers are required to include additional safeguards when participants might be vulnerable for various reasons, including mental disability, but the regulations do not indicate what constitutes mental disability or what these additional protections should be.³⁷ In addition, no subpart of the regulations directly addresses research participation of patients who experience desperation.

Subpart C of the regulations describes protections for prisoners participating in research. Additional protections include representation of prisoner perspectives on the IRB, careful scrutiny of potential benefits of research to guard against undue influence, unbiased participant selection, independence from parole decision making, and arrangements for necessary follow up care.³⁸ In addition, only research with certain purposes—such as

(DOD); (4) Department of Education (ED); (5) Department of Energy (DOE); (6) Department of Health and Human Services (HHS); (7) Department of Homeland Security (DHS); (8) Department of Housing and Urban Development (HUD); (9) Department of Justice (DOJ); (10) Department of Transportation (DOT); (11) Department of Veterans Affairs (VA); (12) Agency for International Development (USAID); (13) Consumer Product Safety Commission (CPSC); (14) Environmental Protection Agency (EPA); (15) National Aeronautics and Space Administration (NASA); (16) National Science Foundation (NSF); (17) Social Security Administration (SSA); and (18) the Central Intelligence Agency (CIA).

³⁴ Office for Human Research Protections (OHRP). (n.d.). Informed Consent FAQs: What should be considered in seeking informed consent from individuals with diminished decision-making capacity? Retrieved February 17, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/seeking-informed-consent-from-individuals-with-diminished-decision-making-capacity.html>.

³⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46, Subparts B, C, D. Other agencies have different protections for vulnerable populations, including the Department of Education's additional protections for children involved in human subjects research, codified at 34 C.F.R. § 97(D); and the Environmental Protection Agency's additional protections for pregnant women and fetuses, codified at 40 C.F.R. § 26.302.

³⁶ *Protection of Human Subjects, HHS*. 45 C.F.R. §§ 46.109, 46.116. Note, however, that the Common Rule provides for the possibility of a waiver of informed consent in certain circumstances. See *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.116(d).

³⁷ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.111.

³⁸ *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46, §§46.304, 46.305.



studying the causes, effects, and processes of incarceration—is permitted to include prisoners.³⁹

E. History of Consent Capacity and Research Ethics

Concern for vulnerable individuals in research is often traced back to revelations of past abuse and mistreatment, such as experiments with institutionalized individuals. In addition, widespread public concern regarding historical examples of psychosurgery provides a good example of the need to integrate ethics and neuroscience as new technologies emerge.⁴⁰ Reflection on this history points out the importance of addressing ethical issues then and now.

Over the last four decades, multiple national advisory bodies have attempted to address the complex issues of research ethics involving those who might lack consent capacity. These include the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in the 1970s and the National Bioethics Advisory Commission (NBAC) in the 1990s.⁴¹ More recently, the Secretary’s Advisory Committee on Human Research Protections (SACHRP) released a 2009 set of recommendations, in this case directed to the Secretary of the Department of Human Health and Services.⁴² The following timeline provides an overview of previous attempts at proposing regulations or guidance to govern research involving individuals who might lack consent capacity. History illustrates the challenge to achieving regulatory change. Response to these proposals has not yet prompted policy change or clarity about how to best protect this potentially vulnerable population.

³⁹ *Protection of Human Subjects*, HHS. 45 C.F.R. Part 46, §46.306.

⁴⁰ PCSBI, (2014, May), [Gray Matters, Vol. 1], op cit., pp. 9-10.

⁴¹ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (1978). *as Mentally Infirm*. Washington, DC: Department of Health, Education, and Welfare. Retrieved February 2, 2015 from http://videocast.nih.gov/pdf/ohrp_research_mentally_infirm.pdf; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (1977). *Psychosurgery*. Washington, DC: Department of Health, Education, and Welfare. Retrieved February 2, 2015 from http://videocast.nih.gov/pdf/ohrp_psychosurgery.pdf; National Bioethics Advisory Commission (NBAC). (1998). *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, Volume 1. Bethesda, MD: NBAC. Retrieved February 3, 2015 from <https://bioethicsarchive.georgetown.edu/nbac/capacity/TOC.htm>.

⁴² Secretary’s Advisory Committee on Human Research Protections (SACHRP). (2009). Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIDR). Retrieved February 3, 2015 from <http://www.hhs.gov/ohrp/sachrp/20090715letterattach.pdf>.



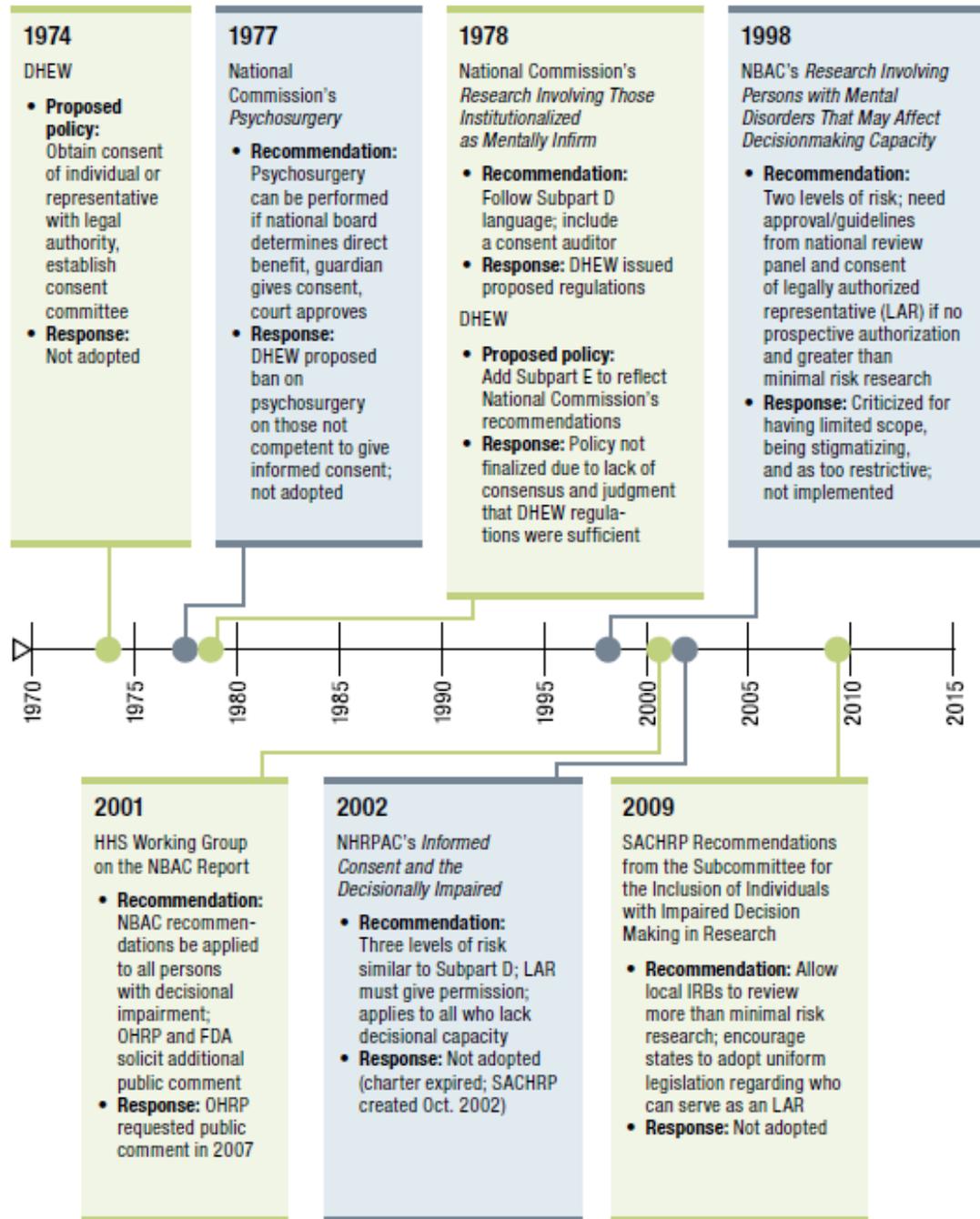


Figure 1: History of Major U.S. Policy Proposals and Recommendations on Consent Capacity in Research

Source: Presidential Commission for the Study of Bioethical Issues (PCSBI). (2015, March). *Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society*. Washington, DC: PCSBI, p. 146, Appendix I: History of Major U.S. Policy Proposals and Recommendations on Consent Capacity in Research.



F. Bioethics Commission Recommendations

In *Gray Matters*, Vol. 2, Recommendations 6, 7, 8, and 9 concern core ethical considerations surrounding capacity, the consent process, and participation in research:

Recommendation 6: Responsibly Include Participants with Impaired Consent Capacity in Neuroscience Research

Researchers should responsibly include individuals with impaired consent capacity who stand to benefit from neuroscience research. Participation, with ethical safeguards in place, can ensure progress aimed at understanding and ameliorating neurological disorders and psychiatric conditions.

Recommendation 7: Support Research on Consent Capacity and Ethical Protections

Funders should support research to address knowledge gaps about impaired consent capacity, including the concept of capacity, brain function and decision-making capacity, current policies and practices, and assessment tools.

Recommendation 8: Engage Stakeholders to Address Stigma Associated with Impaired Consent Capacity

Funders and researchers should engage stakeholders, including members of affected communities, to build understanding of consent capacity and associated diagnoses to mitigate the potential for stigma and discrimination.

Recommendation 9: Establish Clear Requirements for Identifying Legally Authorized Representatives for Research Participation

State legislatures and federal regulatory bodies should establish clear requirements to identify who can serve as legally authorized representatives for individuals with impaired consent capacity to support their responsible inclusion in research.



IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at www.bioethics.gov under "Projects"):

Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society, (Gray Matters, Vol. 1) pp. 9-10 ("Deep Brain Stimulation Research and the Ethically Difficult History of Psychosurgery").

Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Science, (Gray Matters, Vol. 2) pp. 19-25 ("Background and the Promise of Neuroscience").

Gray Matters, Vol. 2, pp. 56-61 ("Ethical Analysis").

Gray Matters, Vol. 2, pp. 65-74 ("Additional Ethical Safeguards").

Gray Matters, Vol. 2, pp. 75-78 ("Gaps in Our Understanding of Consent Capacity and Additional Protections").

V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of research with vulnerable populations highlighted in *Gray Matters*. 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. What does it mean to describe adults whose consent capacity might be absent, impaired, fluctuating, or in question as a vulnerable population?

Starting points for discussion:

- a. Individuals can be vulnerable because they lack the capacity to understand and decide for themselves whether to participate in research and assume the risks of doing so.



- b. Different individuals diagnosed with the same neurological condition, including cognitive impairments, can experience highly varied symptoms. While some individuals might have consent capacity, others might not.
 - c. Individuals with potentially impaired consent capacity are vulnerable to exclusion from research or discrimination when social attitudes involve stigmatizing assumptions about what decisions they can and cannot make based solely on a diagnosis.
 - d. Labeling those with specific diagnoses as vulnerable can be potentially stigmatizing by reinforcing gross generalizations about large and varied groups.
 - e. Labeling a population or individuals as vulnerable has practical implications, such as what additional protections might be warranted to protect these participants.
- 2. Why is it important for research to be conducted on conditions that can lead to impaired consent capacity and why might it be ethically important to include vulnerable individuals?**

Starting points for discussion:

- a. Neurological disorders are a substantial source of morbidity (rates of illness) and mortality (rates of death) in the United States and globally.
 - b. Neurological disorders constitute a substantial burden of disease, which is expected to increase in the future. For example, the United States population is aging, and will increasingly confront neurodegenerative illnesses like Alzheimer's disease. Advances in neuroscience could lead to better knowledge, diagnosis, or treatment of such conditions.
 - c. To advance research that seeks to ameliorate neurological disorders, affected individuals must be included in research responsibly. Responsible inclusion entails compliance with existing regulations, and the use of appropriate additional safeguards, which can vary, depending on the nature of the research and the population being studied.
- 3. How does the current legal and regulatory framework address research involving individuals with impaired consent capacity? Are there any gaps?**



Starting points for discussion:

- a. The Common Rule requires additional safeguards when research participants might be vulnerable for various reasons, including mental disability, but the regulations do not indicate what constitutes mental disability or what these additional protections should be.
- b. The Common Rule requires permission from a legally authorized representative (LAR) if research participants cannot provide their voluntary informed consent. State laws govern who can serve as an LAR, but a dearth of federal regulations and state laws explicitly indicating who can serve as an LAR in research when a prospective research participant lacks consent capacity leads to uncertainty.

4. What are some additional protections and how do they safeguard vulnerable populations participating in neuroscience research?

Starting points for discussion:

- a. Relevant safeguards might include assessment of consent capacity, solicitation of assent and respecting dissent, use of independent monitors, limits on allowable risk, processes to designate and seek involvement of a legally authorized representative, research advance directives, and stakeholder engagement.
- b. Additional protections serve to safeguard vulnerable populations by preventing exploitation. In addition, ethical research practices can help mitigate stigma and discrimination.
- c. There are remaining gaps in our understanding of how and whether various additional protections work. Research is needed to develop ways to evaluate additional protections in practice and innovate new ways to protect vulnerable participants.

5. What are some of the remaining gaps in our understanding of consent capacity and additional protections for vulnerable populations? How can integration of ethics and neuroscience help address these gaps?

Starting points for discussion:

- a. Although consent capacity is generally understood to encompass multiple factors, including the ability to understand information, appreciate its



significance, use information to reason, and make and express a choice about participation, advances in neuroscience reveal that consent capacity should also account for other aspects that might influence decisions. Conceptual research on gaps in our knowledge, including the influence of vulnerability, desperation, and affective states on decision making, could lead to better protections for all research participants.

- b. Empirical questions include how to measure or assess an individual's consent capacity. Researchers must know what abilities to assess to develop good assessment tools.
- c. Practical questions concern how to implement appropriate additional protections. Such questions often have conceptual, empirical, and ethical elements. For example, researchers and those responsible for research oversight must consider why certain protections are justified or required and must also evaluate whether or how well these protections work.

VI. Problem-Based Learning

Scenario A. *Dr. Selleck is seeking participants for a clinical trial testing a new drug to delay the rate of progression of Alzheimer's disease. Participants in the trial would include individuals in the middle stages of Alzheimer's disease who exhibit fluctuating consent capacity. The proposed clinical trial will need to recruit some institutionalized participants from local hospitals or assisted living facilities in order to achieve a large enough sample size to reach sound scientific conclusions. Dr. Selleck's proposal includes seeking consent from those participants who are capable and seeking the permission of legally authorized representatives of those whose capacity is impaired or fluctuating. The director of an assisted living facility, Ms. Wilson, objects to these patients participating in the clinical trial. She argues that the residents at her institution are vulnerable and ought not be included in research, even for "noble" purposes.⁴³*

The following additional readings will be useful in considering this scenario:

Community Engagement Background Module. The module is available at www.bioethics.gov/education.

1. Why might the residents of Ms. Wilson's institution be considered vulnerable or in need of additional protections? Compare and contrast this scenario to the

⁴³ Case adapted from Thomas, J.E., and W.J. Waluchow. (1998). *Well and Good: A Case Study Approach to Biomedical Ethics*. Third Edition. Toronto, Canada: Broadview Press, pp. 129-138.



Willowbrook Hepatitis Study (see the Vulnerable Populations Background module, p. 7).

Starting points for discussion:

- a. The residents might be considered institutionalized. Historically, research ethics violations that might have resulted from the vulnerability associated with institutionalization have coincided with concerns about consent capacity.
- b. Patients with Alzheimer's disease often experience fluctuating or diminishing consent capacity.
- c. The Willowbrook Hepatitis Study involved the vulnerable population of children, not adults who might have impaired consent capacity.

2. Stakeholder and community engagement can help improve research practices, build relationships, and increase the likelihood that research findings are relevant for affected communities. How might engagement provide these residents with additional protection if they are vulnerable? Who should be included in discussions about whether this research should go forward, and at what point in the research process should they be consulted? Use the Community Engagement Background module to consider different possibilities.

Starting points for discussion:

- a. Stakeholders could be engaged at various points during the research process. Researchers should consider thoughtfully which communities are affected by either research or implementation of research findings.
- b. Community-engaged research is a mechanism that involves members of the community in the planning and execution of research, inclusive of those who will be affected by or who are in a position to influence the course of research.
- c. Seeking out the perspectives of underrepresented and potentially stigmatized groups likely to be involved in research, or affected by its results, can bridge different expectations in neuroscience research.
- d. Current federal regulations require that IRBs possess the necessary professional competence to review research activities, either through IRB members with appropriate experience and expertise or invited consultants.



3. What additional protections might need to be in place before this research could go forward?

Starting points for discussion:

- a. The current legal and regulatory framework does not specify which additional protections should be in place for specific research. IRBs oversee the specifics in a proposed research protocol and can help guide selection of additional protections.⁴⁴
- b. Relevant safeguards might include assessment of consent capacity, use of independent monitors, setting limits on allowable risk, processes to designate and seek involvement of a legally authorized representative, research advance directives, and stakeholder engagement.
- c. Seeking participants' assent and respecting dissent in accordance with ethical principles might be particularly relevant to conducting dementia research.⁴⁵

Scenario B. *Traumatic brain injury (TBI), a disruption of normal brain function by impact from an external force, is the leading cause of death and disability among children and young adults. Researchers want to study the effects of a drug that might decrease brain damage in individuals with TBI at various points in time after injury. The proposed study will involve adults who have recently suffered a TBI. Prospective participants will receive either the current standard of care or the experimental intervention. All participants will be monitored at various stages of their recovery period to evaluate the effectiveness of the drug and collect information about side effects.*

1. Should the participants in this study be considered vulnerable?

Starting points for discussion:

- a. Depending on the severity of their injuries, TBI patients might or might not have impaired cognitive abilities that relate to consent capacity. Different individuals diagnosed with the same neurological condition, including cognitive impairment, can experience highly varied symptoms. While some individuals might have consent capacity, others might not.

⁴⁴ Tovino, S.A. (2013). A "Common" proposal. *Houston Law Review*, 50(3), 787-854.

⁴⁵ Black, B.S., et al. (2010). Seeking assent and respecting dissent in dementia research. *American Journal of Geriatric Psychiatry*, 18(1), 77-85.



- b. Research participants who might have impaired consent capacity can be vulnerable in two different ways. First, they might be inappropriately included in research, when in fact they are unable to provide ethically or legally valid informed consent to participate leaving them vulnerable to exploitation. Second, those who retain consent capacity might be inappropriately excluded from research participation based on mistaken generalizations about their abilities given their TBI diagnosis making them vulnerable to disrespect or stigmatization.

2. How would consent capacity assessment and modified consent processes protect research participants diagnosed with TBI, as a vulnerable group?

Starting points for discussion:

- a. Researchers should consider consent capacity individually, and not make blanket capacity determinations applied to all individuals with TBI. As a result of TBI, some cognitive abilities can be significantly impaired, while other abilities remain relatively intact. Validated assessment tools are available for assessing decisional capacity. Robust capacity assessment before and during research helps ensure that TBI participants with impaired, fluctuating, or diminishing consent capacity are adequately protected.
- b. Consent capacity should be reassessed over the course of the research since consent capacity in TBI patients can fluctuate and might improve or worsen as the individual's condition changes.
- c. The researcher should also pay attention to how information is presented and explained to potential participants. Modifying informed consent processes by simplifying forms, orally explaining study procedures, or using creative strategies, such as multimedia supplements, might improve understanding among participants with certain cognitive or decisional impairments.

3. How would decision making by legally authorized representatives (LARs) protect research participants diagnosed with TBI, as a vulnerable group?



Starting points for discussion:

- a. Participants with impaired consent capacity can be enrolled in certain kinds of research by an LAR (i.e., an individual with legal power to make decisions on behalf of others). Using an LAR is an important way to facilitate inclusion of participants with impaired consent capacity in research, ensuring the just distribution of the benefits that might accrue to individuals with TBI. Because LARs are typically loved ones or caregivers, using an LAR is a reasonable way to protect participants from exploitation and help to represent participant interests.
- b. Because it is often difficult for LARs to make certain decisions on behalf of their loved ones, current practice encourages LARs to make decisions based on a “substituted judgment” standard. Under this standard, out of respect for the now impaired individuals, LARs make decisions based on what the individuals themselves would have chosen. However, this is only possible when the individuals’ prior values and wishes are known to some extent. Most individuals will likely not have arranged LAR decision making in advance, especially for decisions regarding research participation. In such cases, LARs often employ a “best interests standard,” or choices that reflect the individuals’ overall wellbeing.

VII. Exercises

Exercise 1. *In a group, assign roles to members with different perspectives reflecting various stakes in a research protocol that involves participants with fluctuating capacity. Read the Alzheimer’s Association’s “How Clinical Trials Work” page designed to explain the clinical trial process to prospective participants with Alzheimer’s disease.*

The “How Clinical Trials Work” page is available at:

Alzheimer’s Association. (n.d.). How Clinical Trials Work. Retrieved May 14, 2015 from
http://www.alz.org/research/clinical_trials/how_clinical_trials_work.asp.

Stakeholders include, but are not limited to:

- *Researchers*
- *IRB members (including scientists, non-scientists, and community members)*
- *Patient advocates*



- *LARs*
- *Prospective participants*

- 1. What ethical concerns might be identified by each stakeholder?**
- 2. What additional information about the study might each stakeholder want to know?**
- 3. What additional protections might different stakeholders think are necessary? What ethical principles support these protections?**

Exercise 2. *Review the following sections of Gray Matters, Vol. 2, and an excerpt from the relevant regulations and address the questions below.*

Gray Matters, Vol. 2, pp. 96-99 (“Current Use of Neuroscience within the Legal System”).

Gray Matters, Vol. 2, pp. 107-109 (“Challenges of Applying Neuroscience to the Legal System”).

Protection of Human Subjects, HHS. 45 C.F.R. Part 46, Subpart C.

- 1. What potential value might neuroscience research bring to the legal system? What kinds of neuroscience research are likely to include prisoners? What should be done to conduct neuroscience involving prisoners ethically?**
- 2. Consider the fMRI study on psychopathy described on page 98 of the reading, which involved prisoners as participants. Based on the available information about the group to individual (G2I) problem, what ethical concerns do you think IRB members might have about fMRI research including prisoners? What ethical concerns do you think prisoners might have?**
- 3. In this fMRI case, there are questions about prisoners as a vulnerable population in neuroscience research. What responsibility do neuroscientists have to protect prisoners as a vulnerable population? What actions can researchers take to fulfill this responsibility?**



VIII. Glossary of Terms

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)].

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.

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

IX. Additional Resources

Bell, E., et al. (2014). Beyond consent in research: Revisiting vulnerability in deep brain stimulation for psychiatric disorders. *Cambridge Quarterly of Healthcare Ethics*, 23(3), 361-368.

Black, B.S., et al. (2010). Seeking assent and respecting dissent in dementia research. *American Journal of Geriatric Psychiatry*, 18(1), 77-85

Berg, J.W., and P.S. Appelbaum. (1999). Subjects’ Capacity to Consent to Neurobiological Research. In H.A. Pincus, J.A. Lieberman, and S. Ferris (Eds.). *Ethics in*



Psychiatric Research: A Resource Manual for Human Subjects Protection (pp. 81-106). Arlington, VA: American Psychiatric Publishing, p. 95.

Cabrera, L. (2011). They might retain capacities to consent but do they even care? *AJOB Neuroscience*, 2(1), 41-42.

Edens, J.F., et al. (2011). Voluntary consent in correctional settings: Do offenders feel coerced to participate in research? *Behavioral Sciences & the Law*, 29(6), 771-795.

Gong, M.N., et al. (2010). Surrogate consent for research involving adults with impaired decision making: Survey of Institutional Review Board practices. *Critical Care Medicine*, 38(11), 2146-2154

Lebacqz, K. (2005). We sure are older but are we wiser? In *Belmont Revisited: Ethical Principles for Research with Human Subjects*, (pp. 99-111). Childress, J.F., Meslin, E.M., and H.T. Shapiro. (Eds.). Washington, DC: Georgetown University Press.

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

Luebbert, R., et al. (2008). IRB member judgments of decisional capacity, coercion, and risk in medical and psychiatric studies. *Journal of Empirical Research on Human Research Ethics*, 3(1), 15-24.

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

Meninger, H.P. (2001). Authenticity in community: Theory and practice of an inclusive anthropology in care for persons with intellectual disabilities. *Journal of Religion, Disability, & Health*, 5(2-3), 13-28.

Muthappan, P., Forster, H., and D. Wendler. (2005). Research advance directives: Protection or obstacle? *American Journal of Psychiatry*, 162(12), 2389-2391.

Palmer, B.W., et al. (2013). Changes in capacity to consent over time in patients involved in psychiatric research. *British Journal of Psychiatry*, 202(6), 454-458.

Schonfeld, T. (2015). Research Involving Vulnerable Populations: A Critical Analysis. In J.D. Arras, E. Fenton, and R. Kukla (Eds.). *The Routledge Companion to Bioethics* (pp. 238-248). New York, NY: Routledge.



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Sulmasy, D.P., and L. Snyder. (2010). Substituted interests and best judgments: An integrated model of surrogate decision making. *JAMA*, 304(17), 1946-1947.

Tovino, S.A. (2013). A “Common” proposal. *Houston Law Review*, 50(3), 787-854.

Wendler, D., and K. Prasad. (2001). Core safeguards for clinical research with adults who are unable to consent. *Annals of Internal Medicine*, 135(7), 514-523.