



# Informed Consent in *Gray Matters*

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## I. Introduction

In [\*Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society\*](#) (*Gray Matters*, Vol. 1), the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) emphasized that ethics and neuroscience research should be integrated early and explicitly throughout the research endeavor.<sup>1</sup> In [\*Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society\*](#) (*Gray Matters*, Vol. 2), the Bioethics Commission addressed three ethically challenging topics at the intersection of neuroscience and society that illustrate the ethical tensions and societal implications of advancing neuroscience: cognitive enhancement, consent capacity, and neuroscience and the legal system. It sought to clarify the current state of the field, identify common ground, and

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<sup>1</sup> Presidential Commission for the Study of Bioethical Issues (PCSBI). (2014, May). *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society* (*Gray Matters*, Vol. 1). Washington, DC: PCSBI.



recommend ethical paths forward for informed and productive discourse as neuroscience continues to advance.<sup>2</sup>

The Bioethics Commission acknowledged that many ethical issues raised by neuroscience are not unique to this field but are expressed in heightened relief. For example, ethical issues surrounding informed consent are common across scientific fields.<sup>3</sup> However, scientists who conduct neuroscience-related human subjects research commonly work with individuals whose consent capacity might be absent, impaired, fluctuating, diminished, or in question.<sup>4</sup> This module addresses the informed consent process for research involving participants who might have impaired consent capacity.

## II. Learning Objectives

*After completing this activity, students should be able to:*

1. Describe consent capacity and its relationship to the ethics of human subjects research.
2. Discuss the current regulatory framework and additional ethical protections for research involving individuals with impaired consent capacity.
3. Describe gaps in our understanding of consent capacity and how they can be addressed.

## III. Background

Federal regulations and international codes guide ethical research with human participants and help ensure that research with human participants is designed and conducted consistent with the rights and welfare of participants. They include the U.S. Department of Health and Human Services' (HHS) Federal Policy for the Protection of Human Subjects, Subpart A, which is referred to as the "Common Rule"; the U.S. Food and Drug Administration's (FDA) Protection of Human Subjects regulations; the World Medical Association's Declaration of Helsinki; and the International Conference on Harmonisation's Good

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<sup>2</sup> Presidential Commission for the Study of Bioethical Issues (PCSB). (2015, March). *Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society* (Gray Matters, Vol. 2). Washington, DC: PCSBI.

<sup>3</sup> PCSBI, (2014, May), [Gray Matters, Vol. 1], op cit, p. 4.

<sup>4</sup> PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 54.



Clinical Practice guidelines.<sup>5</sup> These regulations and guidelines require that researchers obtain fully informed consent from research participants, among other protections.<sup>6</sup>

In some cases, obtaining fully informed consent from research participants might not be possible. The ability to provide fully informed consent (i.e., “consent capacity”) is generally thought to include an ability to understand and appreciate the significance of disclosed information, reason and make a choice based on the information, and express the decision. Some individuals have impaired, fluctuating, or diminished consent capacity, and might not be able to provide ethically and legally valid informed consent.<sup>7</sup>

Scientists from many disciplines conduct research to make discoveries about the brain and related neurological disorders. This research to develop preventions, treatments, and cures for neurological disorders, psychiatric conditions, and brain and nervous system injuries sometimes involves participants with impaired consent capacity, which can manifest as a result of the very condition under study.<sup>8</sup> Importantly, not all individuals with these conditions have impaired consent capacity. Additionally, some individuals with diminished consent capacity can understand information and provide informed consent some or all of the time. Researchers need reliable tools to assess participants’ consent capacity.<sup>9</sup>

To reconcile the challenging tension between the need for rigorous research on debilitating neurological diseases and conditions and the need to protect research participants who might be vulnerable because of impaired consent capacity, “such research should only proceed with additional ethical safeguards and protections in place.”<sup>10</sup>

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<sup>5</sup> *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50; World Medical Association (WMA). (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved May 6, 2015 from <http://www.wma.net/en/30publications/10policies/b3/index.html>; International Conference on Harmonisation (ICH). (1996). ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice - E6(R1). Retrieved May 6, 2015 from <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>.

<sup>6</sup> Informed consent is not required for all types of research; some studies are exempt from this requirement or a waiver of informed consent can be granted by an institutional review board (IRB). For example, research that is strictly observational and some historical studies might not require informed consent of participants.

<sup>7</sup> Appelbaum, P.S., and T. Grisso. (1995). The MacArthur Treatment Competence Study. I: Mental illness and competence to consent to treatment. *Law and Human Behavior*, 19(2), 105-126 PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 54.

<sup>8</sup> Labuzetta, J.N., Burnstein, R., and J. Pickard. (2011). Ethical issues in consenting vulnerable patients for neuroscience research. *Journal of Psychopharmacology*, 25(2), 205-210; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 54-56.

<sup>9</sup> PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 54-55.

<sup>10</sup> *Ibid*, pp. 55.



## A. Ethical Analysis

Historical revelations about ethically troubling experiments with individuals institutionalized with mental health disorders and public concern about psychosurgical procedures such as lobotomy have sparked concern for research participants with impaired consent capacity.<sup>11</sup> As a result, human subjects research review committees have struggled to accommodate the dual mission of protecting individuals against exploitation while simultaneously striving to include participants with impaired consent capacity in research studies to help ensure an equitable distribution of research benefits.<sup>12</sup>

The philosophical basis of informed consent lies in the concept of autonomy and the principle of respect for persons. Inclusion of research participants who might have impaired consent capacity reflects the foundational bioethical principle of respect for persons, which recognizes that all people, including those with diminished autonomy, deserve respect. Respect for persons establishes that all individuals engaging in research should be respected as autonomous decision makers to the extent that their decisions reflect autonomy. Those whose autonomy is diminished should be entitled to additional protection.<sup>13</sup>

Respecting individuals who might have impaired, fluctuating, or diminished consent capacity can include respecting expressions of agency, such as the desire to participate in research, that reflect meaningful participant values or preferences; facilitating measures, such as research advance directives, which express an individual's wishes for the future; and making every effort to avoid misidentifying individuals as either capable or lacking consent capacity.<sup>14</sup> When informed consent cannot serve the traditional function of

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<sup>11</sup> 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 May 6, 2015 from [http://videocast.nih.gov/pdf/ohrp\\_research\\_mentally\\_infirm.pdf](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 May 6, 2015 from [http://videocast.nih.gov/pdf/ohrp\\_psychosurgery.pdf](http://videocast.nih.gov/pdf/ohrp_psychosurgery.pdf); Beecher, H.K. (1966). Ethics and clinical research. *New England Journal of Medicine*, 274(24), 1354-1360; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 56.

<sup>12</sup> PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 56.

<sup>13</sup> National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (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. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 57.

<sup>14</sup> Brudney, D. (2009). Choosing for another: Beyond autonomy and best interests. *Hastings Center Report*, 39(2), 31-37; Jaworska, A. (1999). Respecting the margins of agency: Alzheimer's patients and their capacity to value. *Philosophy & Public Affairs*, 28(2), 105-138; Lindemann, H. (2014). *Holding and Letting Go: The Social Practice of Personal Identities*. New York, NY: Oxford University Press; Meninger, H.P. (2001).



informing participants about the ramifications of participation due to impaired consent capacity, researchers and review bodies must identify and establish additional protections to prevent exploitation and proceed ethically with research.<sup>15</sup>

The principles of beneficence, which calls for efforts to secure the wellbeing of others, and public beneficence, which grounds a societal obligation to advance research that can improve the public wellbeing, support inclusive research participation practices.<sup>16</sup> A fundamental tension between under- and overprotection has led to a “pendulum” of human subjects research protections. Unethical research practices have incited reactive ethical and regulatory policies that focus on the risks of research rather than the benefits and lean toward overprotection by excluding potentially vulnerable participants, including those with impaired consent capacity. Today, policy has shifted toward maximizing inclusion. If research practices are inclusive, the benefits of research can accrue to affected populations, including individuals with impaired consent capacity. However, researchers must walk a fine line between inclusion and protection—policies that maximize inclusion might discount the risks of participation or increase the risk of exploitation.<sup>17</sup>

Neuroscience research has the potential to find ways to prevent, diagnose, and treat disorders that can lead to cognitive impairments. Failing to support research on certain disorders because potential research participants might have impaired consent capacity could be a detriment to current and future patients.<sup>18</sup> The principle of beneficence also grounds a duty to safeguard vulnerable populations from harm and undue risk in research by affording them additional protections.<sup>19</sup> Furthermore, inclusive research participation

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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; Berghmans, R.L.P. (1998). Advance directives for non-therapeutic dementia research: Some ethical and policy considerations. *Journal of Medical Ethics*, 24(1), 32-37; 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; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 57.

<sup>15</sup> PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 59.

<sup>16</sup> National Commission, *The Belmont Report*, op cit; Presidential Commission for the Study of Bioethical Issues (PCSBI). (2010, December). *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*. Washington, DC: PCSBI, pp. 24-25; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 57-58.

<sup>17</sup> 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; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 59-60.

<sup>18</sup> Appelbaum, P.S. (2002). Involving decisionally impaired subjects in research: The need for legislation. *American Journal of Geriatric Psychiatry*, 10(2), 120-124; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 57-58.

<sup>19</sup> National Commission, *The Belmont Report*, op cit; Presidential Commission for the Study of Bioethical Issues (PCSBI). (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSBI, p. 30.



practices allow for a fair distribution of research benefits. The principle of justice requires that research benefits and burdens be distributed equitably across society.<sup>20</sup>

## B. Current Regulatory Framework

No federal regulations specifically address research with adults who have impaired consent capacity.<sup>21</sup> The Common Rule requires permission from a legally authorized representative (LAR) if research participants cannot provide their voluntary informed consent and additional safeguards for individuals “likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.”<sup>22</sup> However, it does not provide information about the nature of such safeguards or protections.<sup>23</sup>

The HHS Office for Human Research Protections (OHRP) provides some guidance about how federal regulations apply to individuals with impaired consent capacity. The guidance notes that LARs can enroll individuals with impaired consent capacity into research protocols and emphasizes that the Common Rule requires that institutional review boards (IRBs) possess the necessary professional competence to review research activities involving individuals with impaired consent capacity.<sup>24</sup> The National Institutes of Health (NIH) also provides researchers and IRBs with points to consider when conducting research involving individuals with potentially impaired consent capacity.<sup>25</sup>

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<sup>20</sup> National Commission, *The Belmont Report*, op cit; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 58.

<sup>21</sup> PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 61-64.

<sup>22</sup> *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.111(a)(4); *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.111(b).

<sup>23</sup> *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.

<sup>24</sup> Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: What should be considered in seeking informed consent from individuals with diminished decision-making capacity? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/seeking-informed-consent-from-individuals-with-diminished-decision-making-capacity.html>; Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: When may a legally authorized representative provide consent on behalf of an adult with diminished decision-making capacity? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-provide-consent-adult-diminished-decision-making-capacity.html>; Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 64.

<sup>25</sup> National Institutes of Health (NIH) Office of Extramural Research. (2009). Research Involving Individuals with Questionable Capacity to Consent: Points to Consider. Retrieved May 6, 2015 from <http://grants.nih.gov/grants/policy/questionablecapacity.htm>; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 63.



FDA regulations have similar requirements.<sup>26</sup> FDA's 2014 draft guidance on informed consent for research includes a section addressing research involving participants with impaired consent capacity. The draft guidance leaves the decision about whether to enroll individuals with impaired consent capacity in research to IRBs and investigators and provides points to consider when enrolling such participants in clinical studies.<sup>27</sup>

Federal regulations rely on state laws to dictate who can clearly serve as an LAR.<sup>28</sup> Some states specifically address who can provide consent for an individual with impaired capacity to consent. However, laws vary by state and often address decisions about medical care, not enrollment in research.<sup>29</sup> Importantly, consent for research differs from consent for treatment. Informed consent for medical care involves clinicians seeking permission to treat patients, who, by consenting, agree to accept risks related to treatment in light of the anticipated benefits they might receive. Informed consent in the research setting involves researchers educating prospective participants and their LARs about a proposed study and seeking their consent to participate. In this context, participants or their LARs agree to accept risk for the benefit of others and not, generally, for their own benefit.

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

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<sup>26</sup> *Protection of Human Subjects, FDA*. 21 C.F.R. § 56.107; 21 C.F.R. § 50.20.

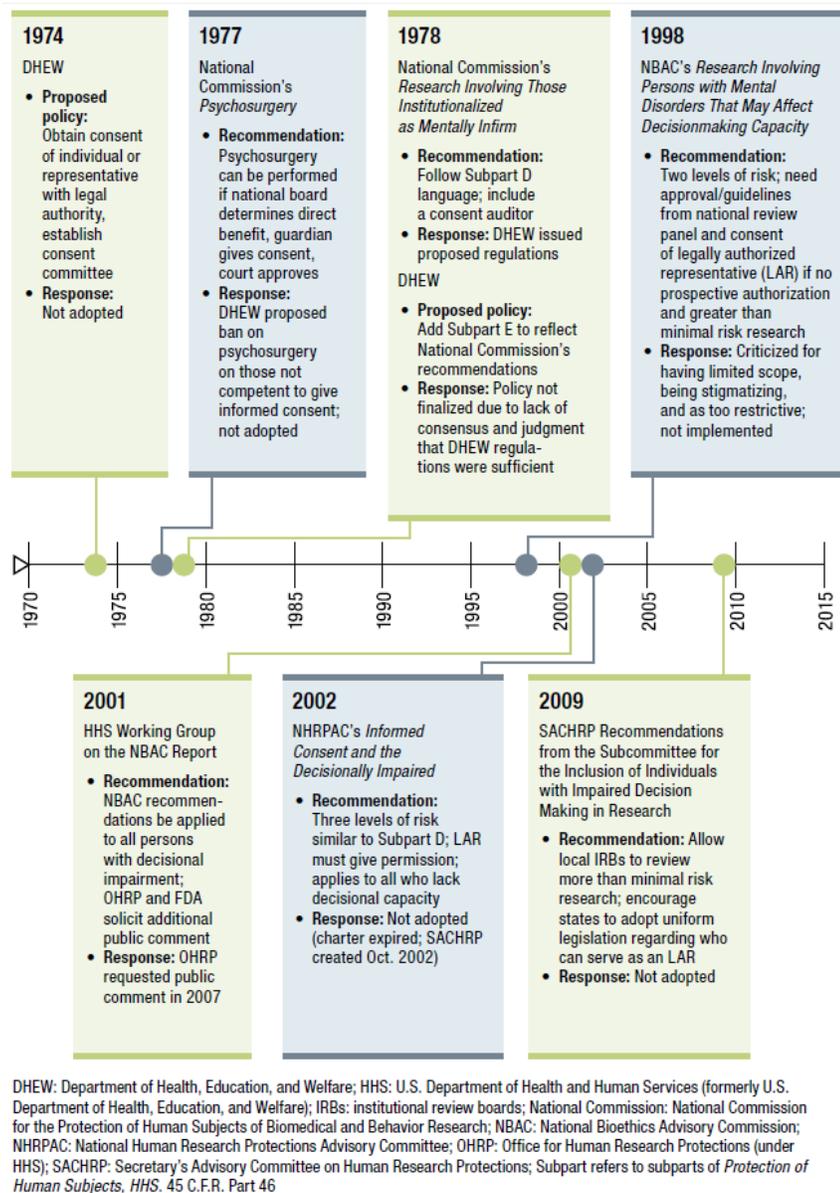
<sup>27</sup> U.S. Food and Drug Administration (FDA). (2014). Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors. Draft Guidance. Retrieved May 6, 2015 from <http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm#impaired>.

<sup>28</sup> *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.102(c); Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>.

<sup>29</sup> Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>; Hoffman, D.E., and J. Schwartz. (1998). Proxy consent to participation of the decisionally impaired in medical research—Maryland's policy initiative. *Journal of Health Care Law & Policy*, 1(1), 123-153, pp. 125-129; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, pp. 65, 71.



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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.

Multiple advisory bodies in the last four decades have attempted to establish uniform guidelines and safeguards to provide clarity and ensure ethical research involving adults who have impaired consent capacity.<sup>30</sup> However, none has led to regulatory change (see

<sup>30</sup> See National Bioethics Advisory Commission (NBAC). (1998). *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*. Volume 1. Bethesda, MD: NBAC. Retrieved May 6, 2015 from <https://bioethicsarchive.georgetown.edu/nbac/capacity/TOC.htm>; Secretary's Advisory Committee on Human Research Protections (SACHRP). (2009). Recommendations from the Subcommittee for the



Figure 1). The current lack of clarity leads to uncertainty and considerable variability in IRB policies and practices.<sup>31</sup> A dearth of federal regulations and state laws indicating who can legally serve as an LAR when a prospective research participant lacks consent capacity leaves a gap in research protections.<sup>32</sup>

### C. Additional Ethical Safeguards

Federal regulations and international codes call for additional ethical safeguards for vulnerable populations, including adults with impaired consent capacity.<sup>33</sup> Relevant safeguards regarding informed consent include modifying informed consent processes, soliciting participant assent and respecting dissent, using independent consent monitors, designating and seeking permission from an LAR, completing research advance directives, and engaging stakeholders, among others.

Researchers can modify the informed consent process to improve comprehension among participants with impaired consent capacity by simplifying forms, orally explaining study procedures and other pertinent information, or using other creative strategies such as multimedia presentations of consent materials. Additional research to better understand and assess consent capacity might lead to additional enhanced informed consent strategies.<sup>34</sup>

When participants cannot provide valid informed consent, researchers must obtain consent from an LAR. However, researchers should include the participant in the informed consent process to the extent possible. For example, they should seek participant assent and respect dissent. Although obtaining assent is not the ethical or legal equivalent of obtaining informed consent, expressing assent allows participants lacking consent capacity to meaningfully communicate desires regarding research procedures. Additionally, respecting

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Inclusion of Individuals with Impaired Decision Making in Research (SIIDR). Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/sachrp/20090715letterattach.pdf>; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 61-65, 146.

<sup>31</sup> 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; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 65.

<sup>32</sup> Appelbaum, P.S., op cit; Gong, M.N., et al., op cit; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 71.

<sup>33</sup> *Protection of Human Subjects, HHS*. 45 C.F.R. § 46; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50; World Medical Association (WMA), op cit.

<sup>34</sup> 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; Kaup, A.R., et al. (2011). Decisional capacity to consent to research in schizophrenia: An examination of errors. *IRB*, 33(4), 1-9; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 67.



dissent maintains the dignity of research participants and protects participants from burden and discomfort.<sup>35</sup>

Federal regulations allow for independent third parties to observe the consent process. Independent consent monitors can help researchers consider and address ethical challenges that arise during the informed consent process. They also can facilitate the assessment of consent capacity and monitor assent and dissent of research participants with impaired consent capacity throughout the research process.<sup>36</sup>

LARs, also known as surrogate or proxy decision makers, have the legal authority to make decisions on behalf of someone else.<sup>37</sup> Using LARs can facilitate inclusion of participants with impaired consent capacity in research and ensure “the just distribution of the benefits that might accrue to people who share the disorder under study.”<sup>38</sup> It also can protect participants from exploitation, as loved ones and caregivers are usually designated as LARs and “are often the best proxy for representing participant interests.”<sup>39</sup>

Although most commonly used to delineate preferences about future health care, advance directives also can help in the informed consent process for research. Advance directives are documents that specify an individual’s desire or willingness to participate in certain research should their consent capacity become impaired at a later date, and can include designation of an LAR. However, there can be practical and ethical challenges associated with research advance directives. For example, questions remain about how closely wishes regarding research participation expressed previously by a competent individual should be honored when they conflict with later statements of that same individual whose consent capacity has become impaired.<sup>40</sup>

Finally, stakeholder and community engagement can help improve informed consent processes. Individuals with impaired consent capacity might identify with underrepresented

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<sup>35</sup> Black, B.S., et al. (2010). Seeking assent and respecting dissent in dementia research. *American Journal of Geriatric Psychiatry*, 18(1), 77-85; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 67.

<sup>36</sup> National Institutes of Health (NIH) Office of Extramural Research. (2009). Research Involving Individuals with Questionable Capacity to Consent: Points to Consider. Retrieved May 6, 2015 from <http://grants.nih.gov/grants/policy/questionablecapacity.htm>; Gupta, U.C., and S. Kharawala. (2012). Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations. *Perspectives in Clinical Research*, 3(1), 8-15; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 68-69.

<sup>37</sup> *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.111(a)(4); 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; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 64-65, 70-72.

<sup>38</sup> PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 71.

<sup>39</sup> Ibid.

<sup>40</sup> Muthappan, P., Forster, H., and D. Wendler. (2005). Research advance directives: Protection or obstacle? *American Journal of Psychiatry*, 162(12), 2389-2391; Appelbaum, P.S., op cit; Jaworska, A., op cit; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 73-74.



and stigmatized groups; engaging with community members likely to be involved in research or affected by its results can build relationships and trust among researchers and potential participants, bridge differing expectations of neuroscience research, and mitigate stigma by helping researchers avoid the assumption that all individuals with a certain disorder have impaired consent capacity.<sup>41</sup>

Consent capacity is task-specific. An individual's capacity to consent depends on the nature and complexity of the decision; one can have capacity to consent for certain studies or aspects of studies but not for others. Thus, additional protections should be appropriate for the context and individual.<sup>42</sup>

## D. Gaps in Our Understanding of Consent Capacity

Definitions of consent capacity vary. Addressing the gaps in our knowledge about impairments in consent capacity can increase understanding to improve protections and the informed consent process. For example, the emotional aspects of consent capacity are often overlooked. Some scholars contend that we need to know more about how emotions affect decision making, including individuals' appreciation of risk.<sup>43</sup>

Assessment instruments to evaluate consent capacity vary, in part due to divergent views about what combination of abilities comprise consent capacity. Assessment tools might have different definitions of reasoning, be tailored to specific protocols, and require specific skills and training to administer. Further research to refine assessment tools will help promote the ethical conduct of research involving individuals with impaired consent capacity. Refined assessment tools might be tailored to particular abilities needed for specific research contexts and have designated score thresholds for what qualifies an individual as capable of providing informed consent in that context.<sup>44</sup> Assessment tools should be able to differentiate vulnerability caused by impaired consent capacity and

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<sup>41</sup> Participants in the Community Engagement and Consent Workshop. (2013). Consent and community engagement in diverse research contexts: Reviewing and developing research and practice. *Journal of Empirical Research on Human Research Ethics*, 8(4), 1-18; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, pp. 74, 80-81.

<sup>42</sup> PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 66.

<sup>43</sup> Hindmarch, T., Hotopf, M., and G.S. Owen. (2013). Depression and decision-making capacity for treatment or research: A systematic review. *BMC Medical Ethics*, 14(54), 1-10; Cabrera, L. (2011). They might retain capacities to consent but do they even care? *AJOB Neuroscience*, 2(1), 41-42; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, pp. 75-76.

<sup>44</sup> Dunn, L.B., et al. (2006). Assessing decisional capacity for clinical research or treatment: A review of instruments. *American Journal of Psychiatry*, 163(8), 1323-1334; Appelbaum, P.S., and T. Grisso, op cit; PCSBI, (2015, March), [Gray Matters, Vol. 2], op cit, p. 76.



vulnerability that might result, for example, from desperation for treatment options or confusion about the potential for participation in the research to confer medical benefit—referred to as the therapeutic misconception.<sup>45</sup>

## E. Bioethics Commission Recommendations

Of the 14 recommendations the Bioethics Commission made in *Gray Matters*, Vol. 2, four pertain to consent capacity and the informed consent process.

### **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.**<sup>46</sup>

### **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.**<sup>47</sup>

### **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.**<sup>48</sup>

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<sup>45</sup> 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; 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; PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, p. 76.

<sup>46</sup> PCSBI, (2015, March), [*Gray Matters*, Vol. 2], op cit, pp. 6, 78.

<sup>47</sup> Ibid, pp. 6, 79.

<sup>48</sup> Ibid, pp. 7, 80.



### **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.**<sup>49</sup>

## **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](http://www.bioethics.gov) under "Projects"):

*Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society*, pp. 53-83 ("Capacity and the Consent Process").

## **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 informed consent that are highlighted in *Gray Matters*. Important points are noted with each question to help the instructor guide group discussion. The "Additional Resources" section is a helpful source in answering these questions.

### **1. What is consent capacity? What is its relevance in the ethics of human subjects research?**

Starting points for discussion:

- a. Consent capacity is generally thought to include an ability to understand and appreciate the significance of disclosed information, and to reason and make and express a choice based on that information.
- b. Informed consent is a core pillar of research protections, based in respect for persons. When informed consent is not possible because of impaired consent capacity, additional protections are needed for participation to move forward.
- c. Inclusion of research participants who might have an impaired consent capacity reflects the foundational bioethical principle of respect for persons, which

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<sup>49</sup> Ibid, pp. 7, 82.



recognizes that all people, including those who lack autonomy, deserve respect. Respect for persons establishes that autonomous decision makers should be respected by obtaining their informed consent to participate in research and, if research participants are individuals with diminished autonomy, that they are entitled to additional protection.

- d. The principles of beneficence, which calls for efforts to secure the wellbeing of others, and public beneficence, which grounds a societal obligation to advance research that can improve the public wellbeing, support inclusive research participation practices. If research practices are inclusive, the benefits of research can accrue to affected populations, including individuals with impaired consent capacity. The principle of beneficence also grounds a duty to safeguard vulnerable populations from harm and undue risk in research by affording them additional protections.
- e. Inclusive research participation practices allow for a fair distribution of research benefits. The principle of justice requires that research benefits and burdens be distributed equitably.

## **2. How does the current legal and regulatory framework address research involving individuals with impaired consent capacity? How might it be improved?**

Starting points for discussion:

- a. The Common Rule requires permission from a legally authorized representative (LAR) if research participants cannot provide their voluntary informed consent. A dearth of federal regulations and state laws indicating who can serve as an LAR when a prospective research participant lacks consent leads to uncertainty.
- b. The Common Rule requires additional safeguards for individuals with diminished autonomy. However, it does not provide information about the nature of such safeguards or protections.
- c. The current legal and regulatory framework does not specifically address research involving individuals with impaired consent capacity. Its lack of clarity leads to uncertainty and considerable variability in IRB policies and practices.
- d. The Bioethics Commission recommended that state legislatures and federal regulatory bodies supplement the current regulations by establishing clear requirements to identify who can serve as legally authorized representatives for individuals with impaired consent capacity to support their responsible inclusion in research.



- e. The Bioethics Commission acknowledged consent capacity is task-specific. An individual's capacity to consent depends on the nature and complexity of the decision; one can have capacity to consent for certain studies (or certain aspects of a study) but not for others. Thus, additional protections should be appropriate for the context and individual.

### **3. How might additional protections promote the ethical conduct of research involving individuals with potentially impaired consent capacity?**

Starting points for discussion:

- a. Modifying informed consent processes by simplifying forms, orally explaining study procedures and other pertinent information, or using other creative strategies such as multimedia supplements can improve comprehension among participants with impaired consent capacity and allow them to meaningfully contribute to the informed consent process.
- b. Soliciting participant assent and respecting dissent allows participants lacking consent capacity to meaningfully communicate desires regarding research procedures. Additionally, respecting dissent maintains the dignity of research participants and protects participants from burden and discomfort.
- c. Using independent consent monitors can help researchers consider and address ethical challenges that arise during the informed consent process. They also can facilitate the assessment of consent capacity and monitor assent and dissent of research participants with impaired consent capacity throughout the research process.
- d. Designating and seeking permission from an LAR can facilitate responsible inclusion of participants with impaired consent capacity in research. It also can protect participants from exploitation, as loved ones and caregivers are usually designated as LARs and often have participants' best interests in mind.
- e. Completing research advance directives can help in the informed consent process by allowing individuals to specify a desire to participate in certain research should their consent capacity become impaired at a later date.
- f. Engaging stakeholders and community members can help improve informed consent processes by fostering relationships and trust among researchers and potential participants, bridging differing expectations of neuroscience research, and mitigating stigmatization by helping researchers avoid the assumption that individuals have impaired consent capacity because of their disorder.



#### **4. What are some of the gaps in our understanding of consent capacity? How can they be addressed?**

Starting points for discussion:

- a. Definitions of consent capacity vary. Further research on the causes of impairments in consent capacity could be used to improve the informed consent process.
  - i. For example, the emotional aspects of consent capacity are often overlooked. Some scholars contend that we need to know more about how emotions play a role in decision making, including how emotions can affect individuals' appreciation of risk.
- b. Instruments to assess consent capacity vary. Assessment tools might have different definitions of reasoning, be tailored to specific protocols, and require specific skills and training to administer.
  - i. For example, refined assessment tools might be tailored to specific capacities needed for specific research contexts and have score thresholds for what qualifies an individual as capable of providing informed consent in that context.

## **VI. Problem-Based Learning**

**Scenario A.** *Impairments in consent capacity can manifest in varied ways. In 1998, the National Bioethics Advisory Commission (NBAC) identified four types of limitations in decision-making capacity in its report Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity.*

The following additional reading might be useful in considering this scenario:

National Bioethics Advisory Committee (NBAC). (1998). *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*. Volume 1, Chapter One – An Overview of the Issues: Informed Consent and Decisional Impairment. Bethesda, MD: NBAC. Retrieved May 6, 2015 from <https://bioethicsarchive.georgetown.edu/nbac/capacity/Overview.htm#Consent>.

#### **1. What are the four types of decisional limitations enumerated by NBAC?**

Starting points for discussion:



- a. Fluctuating capacity—also known as a waxing and waning ability to make decisions.
- b. Prospective incapacity—due to the course of an individual's disease or nature of the treatment for the disease, injury, or condition, impaired consent capacity can be predicted to occur at a later date.
- c. Limited capacity—individuals with limited capacity to consent to research can still assent or dissent to research, but cannot provide fully informed consent.
- d. Complete incapacity—the permanent lack of the ability to make decisions which require a significant degree of reflection.

**2. What challenges did NBAC identify that further complicate the consideration of an individual's consent capacity? According to NBAC, how might researchers address these challenges?**

Starting points for discussion:

- a. The four types of decisional limitations—fluctuating, prospective, limited, and complete—serve as a framework for the different ways an individual might have impaired consent capacity. However, some limitations of decision-making capacity might be subtle and hard to identify. Additionally, individuals might exhibit decision-making limitations in different ways.
- b. Two or more of the decisional limitation categories might apply to the same individual. An individual might have prospective incapacity, then experience subtle limitations in their capacity or have fluctuating capacity and finally progress to incapacity.
- c. Circumstantial factors can affect decision-making capacity. For example, some individuals might feel more empowered and in control in certain social situations or when dealing with certain health care professionals or family members.
- d. Researchers should be familiar with the ways that decision-making impairments can manifest and design research with the appropriate protections in place that maximize a participants' ability to decide whether to enroll in or continue in a study.

**3. What open questions regarding research involving individuals with potentially impaired consent capacity did NBAC consider?**



Starting points for discussion:

- a. Our society has not yet decided what degree of impairment qualifies as a lack of consent capacity.
- b. It is very difficult to assess individuals with fluctuating or limited consent capacity, in particular, to determine whether individuals are capable of consenting to research if their capacity is uncertain for long periods.

**4. How might funders of research and researchers continue to address the open questions considered by NBAC?**

Starting points for discussion:

- a. As the Bioethics Commission noted, gaps in our understanding of consent capacity remain, and further research can support the development of best practices for ethical research involving individuals with impaired consent capacity.
- b. The Bioethics Commission recommended that funders 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.
- c. Further research can support the development of innovative protections for participants with impaired consent capacity. Innovative protections might include novel ways to improve participant comprehension of research procedures and creative research designs that tailor informed consent processes based on information gathered during recruitment, among others.

**Scenario B.** *Results of a 2010 survey of U.S. IRB practices reveal a high degree of variability in IRB policies and practices regarding research participation of individuals with an impaired capacity to consent.*

The following additional reading might be useful in considering this scenario:

Gong, M.N., et al. (2010). Surrogate consent for research involving adults with impaired decision making: Survey of IRB practices. *Critical Care Medicine*, 38(11), 2146-2154. Retrieved May 6, 2015 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3939835/>.



**1. The Common Rule relegates the authorization of surrogate decision makers, or LARs, to applicable state laws. However, most states have laws regarding surrogate consent for medical care only, and not for research participation. Why might reliance on health care proxies in lieu of laws regarding surrogate consent for research be problematic?**

Starting points for discussion:

- a. Most individuals do not have an appointed LAR for medical or research decision making.
- b. Many laws on surrogate, or LAR, decision making for medical treatment are limited to certain types of decisions relevant to life-sustaining procedures or to special circumstances such as terminal illnesses or permanent coma.
- c. IRBs might not agree that state laws regarding medical decision making can be extrapolated to decisions regarding research participation.
- d. The standard for medical decision making is different than the standard for research participation due to an expected benefit for the individual. In research, there is often no prospect of direct benefit for the participant.

**2. According to Gong, M.N., et al. (2010), how do IRBs handle the informed consent process for research involving adults whose capacity to consent is impaired?**

Starting points for discussion:

- a. The study found considerable variability in surrogate consent practices between and within individual U.S. states. In practice, IRB acceptance of surrogate consent does not depend on state laws on health care decision making. Some IRBs do not accept surrogate consent for research involving individuals who have impaired consent capacity. For the majority of IRBs that accept surrogates, there was variability in who (e.g., health care proxy, spouse, parent, adult children) could serve as a surrogate.
- b. The study found that many IRBs rarely or never require capacity assessment of research participants. The most common way to assess capacity is asking participants questions informally during the consent process. Few IRBs frequently require cognitive testing or independent monitors.
- c. The study found that most IRBs that accept surrogate consent for research frequently or always require investigators to justify the inclusion of research



participants with impaired consent capacity and respect participant assent or dissent.

- d. The study found that the majority of IRBs request that investigators re-consent the participant if consent capacity returns.
- e. The study found that many IRBs would frequently or always require researchers to obtain permission to continue in a study from the participant if they lose capacity during the course of the study.
- f. The study found that IRBs variably rely on procedures such as the assignment of a research surrogate or the development of an advance research directive.

**3. What standards might help IRBs judge the adequacy of existing practices and guide the development of future policies regarding consent by individuals with an impaired capacity to consent?**

Starting points for discussion:

- a. IRB standards should respect and reflect the views of research participants to the extent possible. For example, previous studies reported that a majority of patients would accept surrogate consent for research should they lose their consent capacity in the future, and would allow their adult children to be their surrogates.<sup>50</sup>
- b. State legislatures and federal regulatory bodies could establish clear requirements to identify who can serve as surrogates for individuals with impaired consent capacity.
- c. IRBs can require additional safeguards such as regular capacity assessments and obtaining assent or dissent and re-consent, among others.
- d. Any clarifications to federal guidance or regulations should be published in leading scientific journals to ensure constructive dialog between IRB members and the scientific community.

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<sup>50</sup> Wendler, D., et al. (2002). Views of potential subjects toward proposed regulations for clinical research with adults unable to consent. *American Journal of Psychiatry*, 159(4), 585-591; Karlawish, J., et al. (2009). Older adults' attitudes toward enrollment of noncompetent subjects participating in Alzheimer's research. *American Journal of Psychiatry*, 166(2), 182-188; Kim, S.Y., et al. (2005). What do people at risk for Alzheimer disease think about surrogate consent for research? *Neurology*, 65(9), 1395-1401; Kim, S.Y., et al. (2009). Surrogate consent for dementia research: A national survey of older Americans. *Neurology*, 72(2), 149-155.



## VII. Exercises

**Exercise A.** *A 2014 post on The Neuroethics Blog hosted by the Center for Ethics in the Neuroethics Program at Emory University (Atlanta, Georgia) considers the elements of ethical informed consent from individuals who might have impaired consent capacity in situations when the investigator stands to gain financially from intellectual property generated from research results but the research participant will not benefit from the research.*

The following reference provides useful information:

Walker, E.F., and A.T. Ryan. (2014, July 15). Intellectual property from clinical research on neuropsychiatric disorders: What constitutes informed consent? *The Neuroethics Blog*. Retrieved May 6, 2015 from <http://www.theneuroethicsblog.com/2014/07/intellectual-property-from-clinical.html>.

- 1. Should consent forms explicitly inform individuals that their participation in research might lead to financial incentives for investigators? Why or why not?**
- 2. How might the informed consent process be improved so that individuals with impaired consent capacity and their LARs comprehend the broader implications of intellectual property rights and what investigators might gain as a result of their participation in a study?**
- 3. Consider that individuals with impaired consent capacity might be less willing to participate in important research if they are informed that the investigators might benefit financially from intellectual property generated from research results. Is this a justification for limiting what information is conveyed during the consent process? Why or why not?**

**Exercise B.** *Research advance directives, although uncommon, might be especially helpful for research in which the prospective participants' consent capacity might predictably become impaired at a later date. However, there are practical challenges and ethical concerns associated with research advance directives.*

The following references provide useful information:

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



Retrieved May 6, 2015 from  
<http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.162.12.2389>.

*Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society*, pp. 6-7 (“Dementia, Personality, and Changed Preferences”).

1. **Find an example of a medical advance directive on the Internet. How might a medical advance directive be revised to a *research* advance directive? Construct your own research advance directive.**
2. **What are some of the obstacles to the use of research advance directives?**
3. **How closely should research advance directives be honored when the current wishes of potential participants, now with impaired consent capacity, seem to conflict with the wishes they expressed on paper before they lost the capacity to consent? Which should take priority: the person who drafted the directive, or the person with a present-day impairment?**
4. **Propose a policy intended to promote the responsible inclusion of individuals who might have impaired consent capacity in research. Does it require or encourage the use of research advance directives? Why or why not?**

## VIII. 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 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.

**Justice:** The social policies, practices, obligations, attitudes, or resultant state of affairs that members of a society owe one another because of what each member deserves. Justice is the ethical principle that calls on us to give others their due, including fairly distributing of burdens and benefits, addressing past wrongs, deterring future wrongs, holding others to their commitments, and recognizing the standing of each member.

**Protocol:** A plan for the conduct of a research project, including all aspects of the project from recruitment to obtaining informed consent to dissemination of results.

**Public beneficence:** The ethical principle that calls on researchers, scientists, and decision-makers to pursue and secure public benefits while minimizing personal and public harm.

**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.

## IX. Additional Resources

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

Appelbaum, P.S. (2002). Involving decisionally impaired subjects in research: The need for legislation. *American Journal of Geriatric Psychiatry*, 10(2), 120-124.

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

Dunn, L.B., et al. (2006). Assessing decisional capacity for clinical research or treatment: A review of instruments. *American Journal of Psychiatry*, 163(8), 1323-1334.



Emanuel, E.J., Wendler, D., and C. Grady. (2000). What makes clinical research ethical? *The Journal of the American Medical Association*, 283(20), 2701-2711.

Gupta, U.C., and S. Kharawala. (2012). Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations. *Perspectives in Clinical Research*, 3(1), 8-15.

Labuzetta, J.N., Burnstein, R., and J. Pickard. (2011). Ethical issues in consenting vulnerable patients for neuroscience research. *Journal of Psychopharmacology*, 25(2), 205-210.

Muthappan, P., Forster, H., and D. Wendler. (2005). Research advance directives: Protection or obstacle? *American Journal of Psychiatry*, 162(12), 2389-2391. Retrieved May 6, 2015 from <http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.162.12.2389>.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (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. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

Gong, M.N., et al. (2010). Surrogate consent for research involving adults with impaired decision making: Survey of IRB practices. *Critical Care Medicine*, 38(11), 2146-2154. Retrieved May 6, 2015 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3939835/>.

Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: What should be considered in seeking informed consent from individuals with diminished decision-making capacity? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/seeking-informed-consent-from-individuals-with-diminished-decision-making-capacity.html>.

Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: When may a legally authorized representative provide consent on behalf of an adult with diminished decision-making capacity? [Webpage]. Retrieved May 6, 2015 from <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-provide-consent-adult-diminished-decision-making-capacity.html>.

Office for Human Research Protections (OHRP). (2011). Informed Consent FAQs: Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject? [Webpage]. Retrieved May 6, 2015 from



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<http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>.

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

*Protection of Human Subjects, HHS. 21 C.F.R. § 50.*

U.S. Food and Drug Administration (FDA). (2014). Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors. Draft Guidance. Retrieved May 6, 2015 from

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm#impaired>.

World Medical Association (WMA). (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved May 6, 2015 from <http://www.wma.net/en/30publications/10policies/b3/index.html>.