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The Revised Common Rule and Mental Illness: Enduring Gaps in Protections

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I. INTRODUCTION

Advances abound in biotechnology and biomedicine, and cutting-edge clinical research is transforming medical practice by the minute.[1] While benefits are quite likely, biomedical research with people who suffer from mental illness[2] must include enhanced protections to guard against harms to this potentially vulnerable population. Notions of harmful, abusive practices in psychiatric research and practice bring to mind the infamous eugenics movement of the early twentieth century;[3] unfortunately, however, abuse is not merely a thing of the distant past. In 2003, a young man with severe mental illness allegedly was coerced by his psychiatrist, against the wishes of his mother, to participate in "the CAFÉ study," a clinical trial comparing atypical antipsychotics, including Seroquel, in first-episode psychosis; the study was conducted within the University of Minnesota Department of Psychiatry and sponsored by AstraZeneca, the manufacturer of Seroquel.[4] In 2004, while still enrolled in the study and taking Seroquel, the young man committed suicide by violent and gruesome means.[5] The State of Minnesota commissioned a 2015 report that showed evidence of coercive enrollment, inadequate supervision of both subjects and study personnel, conflicts of interest, and numerous

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[1] New research in the field of psychiatric genetics and neuroscience may yield valuable discoveries that potentially could lead to better treatments or cures. There is substantial interest in controversial experimentation, such as gene editing and deep brain stimulation, to explore possible treatments and/or cures for mental illness. *See, e.g.*, Alexandra L. Foulkes et al., *Legal and Ethical Implications of CRISPR Applications in Psychiatry*, 97 N.C. L. REV. 1359, 1376 (2019); Ryan E. Lawrence et al., *Patients' Beliefs About Deep Brain Stimulation for Treatment-Resistant Depression*, 9 AM. J. BIOETHICS NEUROSCIENCE 210, 210 (2018). The Author's future work will explore the need for additional human subjects research protections for mentally ill subjects (and their broader community) in genetics and genomics research, and the off-label use of gene-editing biotechnology in the practice of medicine. This Article focuses on current problems in the interpretation and application of revised federal regulations in the context of mentally ill participants in biomedical research. The words "subject" and "participant" are used interchangeably.

[2] Decisively defining "mental illness" is no easy task. "Identifying what counts as a mental illness seems to require some understanding of what counts as mental health, and this may in turn depend on some conception of normal or acceptable behavior, moods, and thought patterns. Thus, an understanding of mental illness is not merely descriptive of actual behavior; it is also prescriptive of what healthy behavior actually is." GARY E. JONES & JOSEPH P. DEMARCO, BIOETHICS IN CONTEXT 416 (2016); *see also Patient Care & Health Information: Diseases & Conditions: Mental Illness: Symptoms & Causes*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/mental-illness/symptoms-causes/syc-20374968 [https://perma.cc/7NAQ-AVM3] (The Mayo Clinic describes mental illness as "a wide range of mental health conditions—disorders that affect your mood, thinking and behavior. Examples of mental illness include depression, anxiety disorders, schizophrenia, eating disorders and addictive behaviors."). Note, too, that there is now a small sector of the community moving to embrace "mental illness" as a part of one's identity, critical of the extent to which psychiatry has pathologized "madness" and challenging "the tendency to adopt, too readily, the (medical) view that madness is inherently disabling." *See., e.g.*, Mohammed Abouelleil Rashed, *In Defense of Madness: The Problem of Disability*, 44 J. MED. & PHIL. 150, 152, 165 (2019).

[3] For example, see Buck v. Bell, 274 U.S. 200, 207 (1927), an antiquated U.S. Supreme Court decision (never overturned and still "good law" in the United States) that wholeheartedly embraced systemic disregard of the human rights and dignity of people allegedly afflicted with mental illness. The Court gave its stamp of approval to the medical establishment's abuse of "imbeciles" or "mental defectives." *Id.* Specifically, in this case Justice Holmes upheld a Virginia eugenic sterilization statute and stated that "three generations of imbeciles" are enough, allowing sterilization of an allegedly mentally ill woman whose mother and daughter also had been designated mentally defective. *Id.* For a detailed overview and analysis of the case, the widely accepted historical abuse of persons with mental illness, and the machinations of the eugenics movement, see PAUL A. LOMBARDO, THREE GENERATIONS, NO IMBECILES: EUGENICS, THE SUPREME COURT, AND BUCK V. BELL (2008).

[4] For a critical report and overview of this research study, *see* STATE OF MINN. OFF. OF THE LEGIS. AUDITOR, A CLINICAL DRUG STUDY AT THE UNIVERSITY OF MINNESOTA DEPARTMENT OF PSYCHIATRY: THE DAN MARKINGSON CASE SPECIAL REVIEW 5-7 (2015).

[5] *Id.* at 7.

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misrepresentations and unethical cover-ups.[6] Though some bioethics and mental health policy professionals have signaled that human research protections for mentally ill people are insufficient,[7] any efforts to remedy deficiencies repeatedly miss the mark. The United States has never promulgated regulations or prescribed strict guidance on concrete approaches to addressing mental health vulnerabilities in clinical research; rather, vulnerability determinations have rested "on a common tradition of interpreting the regulations."[8] This practice continues despite recent changes to the Common Rule.[9]

Shortcomings in the regulatory management of biomedical research with people who suffer from mental illnesses are evident, especially considering the inclination of researchers, in practice, to narrowly focus on a participant's consent-based decision-making capacity.[10] An exclusive focus on a mentally ill person's decision-making capacity—as measured by standardized assessment instruments such as the MacCAT-CR)[11]—when contemplating their vulnerability to coercion or undue influence ignores other sources of vulnerability for this population. These vulnerabilities include the lived experience of low self-esteem resulting from stigma,[12] sometimes being feared[13] or discriminated against,[14] and social isolation.[15] Other contributions to vulnerability in this

[6] *Id.* at 9-10, 17, 19.

[7] As early as 1997, Carl Elliott sounded the alarm that we must consider that "depression often leaves a patient's cognitive abilities intact," but frequently changes their values, thoughts and behaviors, and also may make them less concerned about potential risks of harm to themselves from research. Carl Elliott, *Caring About Risks: Are Severely Depressed Patients Competent to Consent to Research?*, 54 ARCHIVES GEN. PSYCHIATRY 113, 113 (1997). Elliott noted that if his hypothesis is correct, institutional review boards must be charged with taking "special precautions in allowing researchers to enroll depressed patients in research protocols." *Id.* at 114.

[8] James DuBois et al., *Restoring Balance: A Consensus Statement on the Protection of Vulnerable Research Participants*, 102 AM. J. PUB. HEALTH 2220, 2224 (2012).

[9] *See* Revised Common Rule, 45 C.F.R. § 46 (2019).

[10] *See* Corinne Lajoie et al., *The Concept of Vulnerability in Mental Health Research: A Mixed Methods Study on Researcher Perspectives*, 15 J. EMPIRICAL RES. ON HUM. RES. ETHICS 128, 138 (2020) [hereinafter Lajoie et al., *Concept of Vulnerability*].

[11] PAUL S. APPELBAUM & THOMAS GRISSO, MACARTHUR COMPETENCE ASSESSMENT TOOL FOR CLINICAL RESEARCH (MACCAT-CR) iii (2001). The MacCAT-CR is a tool used for assessing a potential participant's capacity to consent to clinical research participation, and focuses on the concepts of understanding, appreciation, reasoning, and ability to express a choice. *Id.* at 1. Notably, in one study severely depressed patients were shown to do remarkably well on the MacCAT-CR, most receiving "perfect or near-perfect scores." Carl Erik Fisher et al., *The Ethics of Research on Deep Brain Stimulation for Depression: Decisional Capacity and Therapeutic Misconception*, 1265 ANNALS OF N.Y. ACAD. SCI. 69, 74 (2012). The study authors argued that "[g]iven the consistency of these findings, the research community should consider whether most individuals with psychiatric disorders are actually as vulnerable to decisional impairments as they are commonly portrayed, or if such concerns might instead be a reflection of the widespread stigma and prejudice against psychiatric disorders." *Id.* The fact that severely depressed patients consistently do well on a test for capacity to consent to research could also indicate that this type of capacity assessment is not the best means for detecting potential vulnerabilities in this population.

[12] Bruce G. Link et al., *Stigma as a Barrier to Recovery: The Consequences of Stigma for the Self-Esteem of People with Mental Illnesses*, 52 PSYCHIATRIC SERVS. 1621, 1623 (2001).

[13] Jo C. Phelan & Bruce G. Link, *Fear of People with Mental Illnesses: The Role of Personal and Impersonal Contact and Exposure to Threat or Harm*, 45 J. HEALTH SOC. BEHAV. 68, 79 (2004).

[14] Evelien P. M. Brouwers, *Social Stigma Is an Underestimated Contributing Factor to Unemployment in People with Mental Illness or Mental Health Issues: Position Paper and Future Directions*, 8 BMC PSYCHOL., no. 38, 2020, at 1, 4.

[15] Karen L. Fortuna et al., *Unmet Needs of People with Serious Mental Illness: Perspectives from Certified Peer Specialists*, 90 PSYCHIATRIC Q. 579, 582-83 (2019); *see also*, Eric R. Wright et al., *Stigma and the Sexual Isolation of People with Serious Mental Illness*, 54 SOC. PROBS. 78, 79 (2007).

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population include underemployment or unemployment,[16] housing insecurity,[17] "limited availability of providers, the affordability of health insurance, and the cost of drugs."[18] Additional sources of vulnerability may include the mental illness itself and psychotropic drugs used to treat the illness, both potentially altering the patient-participant's authentic self through their effects on thought processes and choices.[19] Further, the power imbalance within the psychiatrist-researcher patient-participant relationship—sometimes referred to as "power-relational vulnerability" or deferential vulnerability[20]— is another source of vulnerability that may go unrecognized.[21] Given the history of stigmatization and abuse against mentally ill people, both outside[22] and within the research context,[23] regulations and guidance should impose heightened protections for this population to ensure proper enrollment and continued participation in biomedical research.

To say that *all* potential participants with mental illness *are* vulnerable to coercion or undue influence casts too wide a net.[24] Yet, an approach that views *all*

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[16] Debra Lerner et al., *Unemployment, Job Retention, and Productivity Loss Among Employees with Depression*, 55 PSYCHIATRIC SERVS. 1371, 1371 (2004); *see also*, Brouwers, *supra* note 14, at 4.

[17] John Sylvestre et al., *Poverty and Serious Mental Illness: Toward Action on a Seemingly Intractable Problem*, 61 AM. J. COMMUNITY PSYCHOL. 153, 156 (2018).

[18] Allison C. Nugent et al., *The Ethics of Clinical Trials Research in Severe Mood Disorders*, 31 BIOETHICS 443, 451 (2017).

[19] *See* Elliot, *supra* note 7, at 115; Lisa E. Smilan, *The Off-Label Loophole in the Psychopharmacologic Setting: Prescription of Antipsychotic Drugs in the Nonpsychotic Patient Population*, 30 HEALTH MATRIX: J. L. MED. 233, 273, 302 (2020). On this point, however, it is important to recognize the heterogeneity among mental illnesses, how they affect those who live with them, and the effects of medications on specific illnesses. Dilip V. Jeste & Elyn Saks, *Decisional Capacity in Mental Illness and Substance Use Disorders: Empirical Database and Policy Implications*, 24 BEHAV. SCI. L. 607, 607 (2006). For example, one could argue that a person who suffers from schizophrenia will have their authentic self restored with the aid of antipsychotic medication, whereas, a person without psychotic symptoms but taking an antipsychotic may lose their authentic self to the medication. *See* Jemima Thompson et al., *Experiences of Taking Neuroleptic Medication and Impacts on Symptoms, Sense of Self and Agency: A Systematic Review and Thematic Synthesis of Qualitative Data*, 55 SOC. PSYCHIATRY & PSYCHIATRIC EPIDEMIOLOGY 151, 161 (2020).

[20] David Wendler, *A Pragmatic Analysis of Vulnerability in Clinical Research*, 31 BIOETHICS 515, 517 (2017).

[21] *See* Marion Boulicault & Timothy Emmanuel Brown, *How Relationships Matter: The Need for Closer Attention to Relationality in Neuroethical Studies*, 9 AM. J. BIOETHICS NEUROSCIENCE 235, 235 (2018). The authors of this article used the term "power-relational vulnerability" to describe "the vulnerability a research participant experiences as a result of asymmetrical power relations existing between investigators and participants." *Id.* Laura Weiss Roberts also warned about how "[t]he relationship with the caregiver or researcher . . . may have carefully hidden coercive influences that may be present, for example, when multiple roles or overlapping relationships exist." Laura Weiss Roberts, *Informed Consent and the Capacity for Voluntarism*, 159 AM. J. PSYCHIATRY 705, 709 (2002). This is especially an issue today where clinical trials are sometimes carried out through individual healthcare providers in their offices, in addition to treatment. *See, e.g.*, Jill A. Fisher & Corey A. Kalbaugh, *United States Private-Sector Physicians and Pharmaceutical Contract Research: A Qualitative Study*, 9 PLOS MED., no. 7, 2012, at 2, https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001271 [https://perma.cc/PW9N-AQ52] (discussing clinical research conducted in physicians' offices).

[22] *See, e.g.*, Patrick Robinson et al., *Measuring Attitudes Towards Mental Health Using Social Media: Investigating Stigma and Trivialisation*, 54 SOC. PSYCHIATRY & PSYCHIATRIC EPIDEMIOLOGY 51, 51 (2019) (finding stigma in regards to mental health is a significant barrier for early diagnosis and treatment); Shoji Yokoya et al., *A Brief Survey of Public Knowledge and Stigma Towards Depression*, 10 J. CLINICAL MED. RES. 202, 202 (2018) (finding that thirty percent of participants in the survey had the stigmatizing belief that a weak personality causes depression).

[23] *See, e.g.*, John H. Noble Jr. & Vera Hassner Sharav, *Protecting People with Decisional Impairments and Legal Incapacity Against Biomedical Research Abuse*, 18 J. DISABILITY POL'Y STUD. 230, 230 (2008); *see also*, STATE OF MINN. OFF. OF THE LEGIS. AUDITOR, *supra* note 4, at 2.

[24] Many scholars and researchers alike seem to find it repugnant to even consider saying that all mentally ill people are likely to be vulnerable to coercion or undue influence due to their mental illness. *See*

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vulnerabilities to coercion or undue influence emanating from mental illness as arising *only* in the context of decision-making capacity, at least as this term currently is assessed and applied in practice,[25] is far too narrow. A middle ground is needed to appropriately protect people with mental illness in biomedical research. This issue is complicated and will surely require complex solutions.

This Article does not set out to solve all the problems, but it is an effort to start a conversation, offer observations on the problematic application of the Revised Common Rule ("rCR") in the context of mental illness, and make some initial recommendations. Further, this Article primarily addresses research with psychiatric patients who are not involuntarily hospitalized or experiencing active psychosis and whose decision-making capacities are not obviously compromised.[26] Part II of this Article provides a brief history of the Common Rule and relevant changes in the rCR, highlighting the lack of clarity on the meaning and parameters of "impaired decision-making capacity" and who is "vulnerable to coercion or undue influence" in the context of mental illness. Challenged here are assumptions that impaired decision-making capacity, as currently assessed and applied in practice, is and must be the rCR's exclusive framework for assessing vulnerability to coercion or undue influence in potential participants suffering from mental illness. Part III discusses how the long-awaited changes to the Common Rule provide little clarity on who is vulnerable to coercion or undue influence outside four specifically named categories, what vulnerability of this type looks like, or how such vulnerability should be determined. Part IV maintains that absent firm leadership and guidance from the U.S. Department of Health and Human Services ("HHS"), expertise is needed

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Nugent et al., *supra* note 18, at 447 ("Indeed, we would argue that formally classifying those with mood disorders as a vulnerable population could potentially contribute to stigma and devalue the societal contributions made by these individuals."); *see also*, Lajoie et al., *Concept of Vulnerability*, *supra* note 10, at 140. Why this is so offensive to these professionals, most of whom presumably are not members of this community, is unclear. While some in this patient population may argue that their mental differences are not an illness, it is fair to say that people who are mentally ill generally are considered to be ill, and mental illnesses specifically target the mind—where emotion, thought and information processing are regulated (or not). (Interestingly, for decades few in biomedical ethics, health policy or law balked at the notion that *all* pregnant women are vulnerable in research. *See* Anna C. Mastroianni et al., *The Pathway Forward: Insights on Factors that Facilitate Research with Pregnant Women*, 42 ETHICS & HUM. RES. 2, 2-3 (2020).). A recent study explored perspectives of individuals living with mental illness on the word "vulnerable." Corinne Lajoie et al., *Enriching Our Understanding of Vulnerability Through the Experiences and Perspectives of Individuals Living with Mental Illness*, 26 ACCOUNTABILITY IN RES. 439, 439 (2019) [hereinafter Lajoie et al., *Enriching our Understanding*]. While some participants had some objections to the word "vulnerable" as a label for all individuals living with mental illness, *id.* at 449, some interesting revelations included that "being called vulnerable can be upsetting, but it ultimately holds some truth and is 'something that's really not inaccurate,'" *id.* at 451, and "I find [the term 'vulnerability'] absolutely correct and accurate. It says what it says." *Id.* at 447. Another participant "thought that the use of the term 'vulnerable' to designate individuals living with mental illness was 'sensitive' and . . . seemed like 'an appropriate term' . . . . [S]he [did not] think that using the term in research contexts is stigmatizing given that it's not 'a public label' or something that others outside this context might find out about." *Id.* at 449. She viewed the term "vulnerable" as neither insulting nor stigmatizing. *Id.*

[25] As applied in practice, "decision-making-capacity" as the catch-all category for vulnerability to coercion or undue influence in the context of mental illness precludes a broader understanding of mental illness vulnerabilities (even if this was not the intent of those who drafted the Revised Common Rule).

[26] People with severe intellectual disabilities are also excluded here, as the assumption is that these individuals at no point possessed decision-making capacity required to consent to research. If abided by, the Common Rule and rCR should provide adequate protections for these individuals, as well as those who are experiencing active psychosis. *See* Common Rule, 45 C.F.R. § 46 (1991); Revised Common Rule, 45 C.F.R. § 46 (2019). Involuntarily institutionalized people also should be protected under the existing rules, because of the inherently coercive nature of that environment and the relationship between institutionalized patient and mental health provider. Extant literature addresses involuntarily institutionalized individuals in clinical research. *See, e.g.*, NAT'L COMM'N FOR THE PROT. OF HUM. SUBJECTS OF BIOMEDICAL AND BEHAV. RSCH., RESEARCH INVOLVING THOSE INSTITUTIONALIZED AS MENTALLY INFIRM (1978).

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regarding the unique circumstances of participants in psychiatric research. Part IV also contemplates sources of expertise, e.g., the psychiatrist who treats mental illness, the patient who suffers from and lives with mental illness, and the mentally ill person who already has served as a subject in biomedical mental health research. Part V suggests new language for binding guidance or further rule revisions. A final suggestion is to modify one scholar's proposal to include research subjects in the research review process, proposing that if specific federal research regulations and guidance do not materialize, the next best alternative is to focus on *who* is at the institutional review board ("IRB") table interpreting existing regulations.

II. THE COMMON RULE THEN AND NOW: CHANGES PROVIDE LITTLE CLARITY

A. EFFORTS TO SOLIDIFY PROTECTIONS

Despite several attempts between the 1970s and 1990s to provide greater protections in biomedical research for people suffering from "mental disorders,"[27] the Common Rule's codification in 1991[28] made no mention of people who suffer from mental illness and only mentioned the "mentally disabled."[29] In 1996, the National Bioethics Advisory Commission ("NBAC") began working to study the issue of "mental disorders" in the context of research participation and to formulate possible solutions to address voids in protections.[30] In December 1998, NBAC issued its report, *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*.[31] NBAC limited its inquiry to decision-making capacity, ignoring other types of vulnerability arising in mental illnesses or "mental disorders."[32] NBAC's first recommendation related to IRBs and how, in order to close gaps and extend appropriate protections to people suffering from "mental disorders," IRBs should be tailored to properly represent these potential participants' interests.[33] Specifically, Recommendation I states:

> All IRBs that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being studied. *At least one of these IRB members should be a member of the population being studied, a*

[27] For a detailed overview of concerns and debates, *see* Richard J. Bonnie, *Research with Cognitively Impaired Subjects: Unfinished Business in the Regulation of Human Research*, 54 ARCH. GEN. PSYCHIATRY 105 (1997).

[28] 45 C.F.R. § 46 (1991).

[29] Common notions of "mental disability" bring to mind persons with lower IQs, congenital brain abnormalities or traumatic brain injuries. However, there could be near-genius individuals who suffer from bipolar disorder or major depressive disorder, for example, who may be vulnerable at certain times and under certain circumstances, not due to an inability to think but due to effects the mental illness (and, perhaps, medications used to treat the illness) has on their brains and true selves.

[30] ELISA EISEMAN, NAT'L BIOETHICS ADVISORY COMM'N, CONTRIBUTING TO PUBLIC POLICY 43 (2003). "NBAC's first task was to determine whether there were any important gaps in laws, regulations, guidelines, and practices and then to determine how to plug them." James F. Childress, *An Introduction to NBAC's Report on Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity*, 7 ACCOUNTABILITY RES. 101, 104 (1999).

[31] NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY (1998).

[32] *See id.* at 5.

[33] *Id.* at iii, 53.

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> *family member of such a person, or a representative of an advocacy organization for this population*.[34]

Official guidance based on these 1998 recommendations would have been appropriate, but federal regulators issued no guidance specifically limiting risks to which mentally ill participants might be exposed in biomedical research.[35]

Due to the heterogeneity of people who suffer from mental illnesses, and the variability of mental illnesses even within diagnostic categories, a detailed, one-size-fits-all rule may have been beyond realistic expectation.[36] But the fact that a task is challenging does not warrant avoiding or abandoning attempts to address it. Nearly thirty years after implementation of the original Common Rule, and over twenty years since the NBAC report, rather than mending inadequacies, the recent changes under the rCR[37] have made an already flawed regulatory framework even more out of sync with safeguarding people with mental illness who may need heightened protections in biomedical research. One major shortcoming of the rCR is that it gives IRBs more responsibility and discretion in deciding what it means to have "impaired decision-making capacity," to whom that criteria should apply, and under what circumstances.[38] This approach allows for inconsistencies based on who is sitting at the IRB table on any given day, at any given institution. As discussed later, the IRB can play a significant role in addressing what is lacking in the rCR,[39] so increased IRB responsibility should not be criticized. Yet, IRB discretion in carrying out increased responsibility ad hoc should be curbed, rather than expanded, through binding guidance or modified regulation.

B. Absence of "Mental Illness" in Original and Revised Common Rule

Very early in the rulemaking process, drafts of what would become the original Common Rule referenced the "mentally infirm,"[40] though ultimately this term was deleted from the final rule. The term "mentally disabled" is the closest approximation to mental illness in the original Common Rule.[41] Who was "mentally disabled" or what constituted a mental disability was never properly defined under the original rule, and whether or not it was intended to include people with mental illness is unknown.[42] The Americans with Disabilities Act definition of "disability" includes a "mental impairment that substantially limits one or more major life activities of an individual,"[43] yet the term "mental disability"

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[34] *Id.* (emphasis added). Where the IRB ordinarily does not address protocols involving potential subjects who suffer from a "mental disorder," NBAC recommended that the IRB's discussion should include "two ad hoc consultants who are familiar with the nature of these disorders and with the concerns of the population being studied; *at least one of these consultants should be a member of the population being studied, a family member of such a person, or a representative of an advocacy organization for this population*." *Id.* (emphasis added).

[35] David B. Resnik, The Ethics of Research with Human Subjects 218, 227 (2018).

[36] Resnik points to the diversity within populations living with mental disability or mental illness that makes it not necessarily appropriate to put them in categories: "[S]ome mentally ill or disabled adults may have good decision-making abilities, while others may not. Also, some may be able to make decisions under certain conditions . . . but not [under] others." *Id.* at 227.

[37] Revised Common Rule, 45 C.F.R. § 46 (2019).

[38] *Id.* §§ 46.107, 46.111.

[39] *See infra* Part IV.

[40] *See* Protection of Human Subjects, 38 Fed. Reg. 31,738, 31,738 (proposed Nov. 16, 1973). For a full discussion, see Diane E. Hoffmann et al., *Regulating Research with Decisionally Impaired Individuals: Are We Making Progress?*, 3 DePaul J. Health Care L. 547, 551-556 (2000).

[41] Common Rule, 45 C.F.R. §§ 46.107, 46.111 (1991).

[42] *See* 45 C.F.R. § 46 (1991).

[43] Americans with Disabilities Act, Pub. L. 101-336, § 3, 104 Stat. 327, 330 (1990) (codified as amended at 42 U.S.C. § 12102(1)(A) (2012)).

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has many mainstream connotations, including congenital brain abnormalities and cognitive deficits from brain damage or neurodegenerative disease.[44] The mystery as to the meaning of "mentally disabled" in the Common Rule is moot, as this term was stricken in the recent revision, shown here:

> 45 C.F.R. § 46.107 IRB membership.
>
> (a) . . . If an IRB regularly reviews research that involves a ~~vulnerable~~ category of subjects **that is vulnerable to coercion or undue influence**, such as children, prisoners, ~~pregnant women, or handicapped~~ **individuals with impaired decision-making capacity, or economically** or ~~mentally disabled~~ **educationally disadvantaged** persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these **categories of** subjects.
>
> . . . .
>
> (~~f~~ **e**) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues ~~which~~ **that** require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.[45]

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[44] *See, e.g.*, John Petrila & Thomas Brink, *Mental Illness and Changing Definitions of Disability Under the Americans with Disabilities Act*, 52 PSYCHIATRIC SERVS. 626, 626 (2005) (discussing the relationship between the definition of disability and mental impairment, including organic brain syndrome and learning disabilities); RESEARCH AND TRAINING CTR. ON INDEP. LIVING, GUIDELINES FOR WRITING AND REPORTING ABOUT PEOPLE WITH DISABILITIES (6th ed. 2001) (listing cognitive impairment, learning disability, and more as categories of mental disability).

[45] Revised Common Rule, 45 CFR §§ 46.107(a), 46.107(e) (2018), WL 45 CFR § 46.107 (showing Westlaw comparison of version effective until July 18, 2018 and current version effective July 19, 2018). Other relevant changes in the Revised Common Rule, regarding criteria for IRB approval of research with potentially vulnerable subjects are:

> § 46.111 Criteria for IRB approval of research.
>
> (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
>
> . . . .
>
> (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted ~~and~~. **The IRB** should be particularly cognizant of the special problems of research ~~involving~~ **that involves a category of subjects who are** vulnerable ~~populations~~ **to coercion or undue influence**, such as children, prisoners, ~~pregnant women, mentally disabled persons~~**individuals with impaired decision-making capacity**, or economically or educationally disadvantaged persons.
>
> . . . .
>
> (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, ~~pregnant women, mentally disabled persons~~**individuals with impaired decision-making capacity**, or economically or educationally disadvantaged persons, *additional safeguards have been included in the study to protect the rights and welfare of these subjects*.

45 C.F.R. §§ 46.111(a)(3), 46.111(b) (2018), WL 45 CFR § 46.111 (italics added) (showing Westlaw comparison of version effective until July 18, 2018 and current version effective July 19, 2018).

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Other notable changes in the rCR include the addition of those with "impaired decision-making capacity" as one example of individuals who may be vulnerable to coercion or undue influence, as well as instruction regarding possible IRB composition.[46] Mental illness is mentioned nowhere.[47]

C. Impaired Decision-Making Capacity: An Exclusive Lens for Viewing Mental Illness?

The new but likewise vague concept "impaired decision-making capacity" now substitutes for "mentally disabled."[48] The rCR groups individuals with impaired decision-making capacity with other categories of prospective subjects, "such as children, prisoners, . . . [and] economically or educationally disadvantaged" people, when describing the types of subjects meant to be included in those "vulnerable to coercion or undue influence."[49]

Before the Common Rule revisions, relevant literature and analyses of the propriety of enrolling mentally ill people in research rested primarily on concerns about decision-making capacity.[50] In both the original rule and the rCR, however, the use of "such as" in 45 C.F.R. §§ 46.107, 46.111 indicates that the list of vulnerable groups is neither exhaustive nor final.[51] The rCR allows for subjects who suffer from mental illness but who *do* possess traditional decisional capacity to *not* be considered vulnerable in the clinical research setting. But, intended or not, the rCR's "such as" language also implies that factors besides impaired decision-making capacity may affect a person's vulnerability to coercion or undue influence; that is, *sometimes people who suffer from mental illness*

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[46] *Compare* 45 C.F.R. §§ 46.107, 46.111 (1991) (omitting those with "impaired decision-making capacity" as an example of individuals vulnerable to coercion or undue influence), *with* 45 C.F.R. §§ 46.107, 46.111 (2019) (including those with "impaired decision-making capacity as an example of individuals vulnerable to coercion or undue influence).

[47] *See* 45 C.F.R. § 46 (2019).

[48] In the Preamble to the final revised rule, HHS stated that it was using "'individuals with impaired decisionmaking ability' to replace the term 'mentally disabled persons.'" Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,149, 7,204 (Jan. 19, 2017) (to be codified at 45 C.F.R. pt. 46). HHS stated that some public comments had argued that the term "mentally disabled" was "potentially patronizing." *Id.* One comment had suggested the use of the term "populations with impaired decision making ability" to replace the term "mentally disabled," and HHS adopted this new language and incorporated it in the revised rule. *Id.* Note, too, that HHS stated that the Secretary's Advisory Committee on Human Research Protections (SACHRP) suggested in 2009 the use of the phrase "impaired decisionmaking capacity," but it is not stated what it was to replace or what categories of subjects it should include. *See id.* (citing SACHRP, *Recommendations Regarding Research Involving Individuals with Impaired Decision-Making*, U.S. Department of Health and Human Services (July 15, 2009), https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2009-july-15-letter-attachment/index.html [https://perma.cc/MGZ7-WGUJ]); *see also* Elisa A. Hurley, *From the Director: "Vulnerability" in the Revised Common Rule*, AMP&RSAND: The PRIM&R Blog (Sept. 12, 2017), https://blog.primr.org/vulnerability-revised-common-rule/ [https://perma.cc/Q2ZR-FX3J]. IRBs are tasked with delineating the concept of "impaired decisionmaking capacity" on a protocol-by-protocol basis.

[49] 45 C.F.R. § 46.111(b) (2019).

[50] *See, e.g.*, Paul S. Appelbaum et al., *Competence of Depressed Patients for Consent to Research*, 156 Am. J. Psychiatry 1380, 1381 (1999); Lindy Marie Fields & James Douglas Calvert, *Informed Consent Procedures with Cognitively Impaired Patients: A Review of Ethics and Best Practices*, 69 Psychiatry & Clinical Neurosciences 462, 469 (2015); Gordon MacFarlane et al., *Proposed Guidelines for the Protection of Vulnerable Subjects in Clinical Trials: Protections for Decisionally Impaired Subjects*, 10 Clinical Ethics 59, 60 (2015); Ines Morian-Sanchez et al., *Assessment of Capacity to Consent to Research Among Psychiatric Outpatients: Prevalence and Associated Factors*, 87 Psychiatric Q. 89, 90 (2016); Jeffrey P. Spike, *Informed Consent is the Essence of Capacity Assessment*, 45 J.L. Med. & Ethics 95, 95 (2017); Phillip Yanos et al., *Research Risk for Persons with Psychiatric Disorders: A Decisional Framework to Meet the Ethical Challenge*, 60 Psychiatric Servs. 374, 376 (2009).

[51] 45 C.F.R. §§ 46.107(a), 46.111 (1991); 45 C.F.R. §§ 46.107(a), 46.111 (2019).

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may fairly be considered a vulnerable, unnamed group under the rCR for reasons other than impaired decision-making capacity. Excluding bases outside traditional notions of decisional capacity, as it is assessed and applied in practice, in determining vulnerability to coercion or undue influence in this population makes simplistic and even harmful assumptions about the experience of mental illness.[52] A mentally ill person might possess traditional decision-making capacity based on a standard assessment and *still* be vulnerable to coercion or undue influence in biomedical research, and, thus, need additional, heightened protections.[53]

D. WHY "IMPAIRED DECISION-MAKING CAPACITY" IS TOO LIMITED

Under the rCR, specific categories of subjects deemed to be per se vulnerable to coercion or undue influence—children, prisoners, and economically and educationally disadvantaged people[54]—are readily discernable: a child is a person under age 18, a prisoner is an incarcerated person, and determining a person's financial means and education level is a straightforward task. The same cannot be said of the category "individuals with impaired decision-making capacity."[55] Categories of individuals vulnerable to coercion or undue influence can extend beyond those named in the rule; but, of those explicitly listed, "individuals with impaired decision-making capacity" is the one category with uncertain meaning. What about a person who has impaired decision-making capacity makes them vulnerable to coercion or undue influence? Where does mental illness fall within this category, if at all? Should "mental illness," standing alone, qualify as a non-enumerated category left open under the "such as" language in 45 C.F.R. §§ 46.107, 46.111?[56] As stated above, if a person is mentally ill but has decision-making capacity, they may still be vulnerable to coercion or undue influence under the rCR.

Numerous sources of vulnerability to coercion or undue influence for those suffering from mental illness are less apparent than common understandings of impaired decision-making capacity, yet no less important.[57] Living with mental illness in a society that misunderstands, fears, and stigmatizes mental illness gives rise to all sorts of vulnerabilities to coercion or undue influence.[58] Some of the symptoms experienced by people suffering from mental illness include despair, guilt,[59] "ambivalence, diminished motivation, disengagement, or impulsivity," [60] somatic disturbances, and suicidality.[61]

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[52] Yes, some people with mental illness have impaired decision-making capacity. Many more, especially those with major depressive disorder, may score well in capacity assessments, *see* Fisher, *supra* note 11, at 74, but be vulnerable to coercion or undue influence for other reasons related to their mental illnesses and treatments. While many scholars and researchers argue that it is harmful to put all people with mental illness in one bucket (assuming that they all are vulnerable to coercion or undue influence), surely it is just as harmful to exclude many mentally ill people from the bucket because they happen to be able to provide reasonable and rational answers to questions, even if those answers do not reflect their true values, opinions and judgments.

[53] *See* RESNIK, *supra* note 35, at 219-220; Yanos et al., *supra* note 50, at 377.

[54] 45 C.F.R. §§ 46.107(a), 46.111 (2019).

[55] *Id.*; RESNICK, *supra* note 35, at 217-20.

[56] 45 C.F.R. §§ 46.107(a), 46.111 (2019).

[57] *See, e.g.*, Yanos et al., *supra* note 50, at 376 (recognizing the concept of vulnerability as broad despite focusing on only two interpretations during research).

[58] *See, e.g.*, Fisher et al., *supra* note 11, at 74.

[59] Elliott, *supra* note 7, at 115.

[60] Roberts, *supra* note 21, at 706.

[61] Nugent et al., *supra* note 18, at 443.

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Major depression causes "diminished ability to think or concentrate, or indecisiveness."[62] In 1997, Professor Carl Elliott aptly wrote: "When a person is caught in the grip of depression, his values, beliefs, desires, and dispositions are dramatically different from when he is healthy. In some cases, they are so different that we might ask whether his decisions are truly his."[63] In fact, because "symptoms can cloud a person's judgment," psychiatrists often "advise patients not to make major life choices while experiencing a depressive episode."[64] Further, psychotropic drugs used to treat mental illness may affect thinking, behavior, values, judgment, and risk-taking assessments—in essence, these drugs may alter one's personality, for better or worse—thereby distorting the potential research subject's true self.[65] Furthermore, mental illness can lead to extreme isolation and loneliness,[66] and participation in biomedical research might provide an inappropriate or false sense of belonging and fellowship in a time of psychiatric crisis or ongoing distress.[67] Ultimately, "even the most well-informed and decisionally 'fit' individual cannot realize the spirit of informed consent if his or her 'choice' is inauthentic, symptom driven, compromised, or coerced."[68]

Many scholars concur that people suffering from mental illness or other conditions that impair decision-making capacity should not be enrolled in biomedical research without "sound scientific justification" for their inclusion.[69] Others believe that "[r]esearch decisional capacity" should not be determined by an assigned diagnosis or

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[62] Lawrence et al., *supra* note 1, at 215-16 (citing AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (5th ed. 2013)); *see also* Emily Bell et al., *Beyond Consent in Research: Revisiting Vulnerability in Deep Brain Stimulation for Psychiatric Disorders,* 23 CAMBRIDGE Q. HEALTHCARE ETHICS 361, 362-63 (2014) (examining vulnerability and consent of patients diagnosed with major depression in deep brain stimulation trials).

[63] Elliott, *supra* note 7, at 115.

[64] Lawrence et al., *supra* note 1, at 216. Clouded judgment should qualify as impaired decision-making, but as the regulation is applied, most likely it would not because such nuances would not be picked up in the traditional capacity assessment. As long as the subject was agreeing to participate in the research, this likely would be assumed by the researcher to be a reasonable and rational decision, even if it differed from the subject's prior beliefs (unknown to the researcher), e.g., that participating in research is a very bad idea. Some scholars have advocated in the clinical care setting that current assessments of capacity miss many aspects of how mental illness potentially changes one's choices. *See* Aryeh L. Goldberg, *How Bioethics and Case Law Diverge in Assessments of Mental Capacity: An Argument for a Narrative Coherence Standard*, 11 AM. J. BIOETHICS NEUROSCIENCE 7, 8-9 (2020)*; see also* Lisa E. Smilan & David S. Conklin, *With NCS, the Clinician May Get Stuck in the Past or Lost in the Present*, 11 AM. J. BIOETHICS NEUROSCIENCE 33, 34 (2020). Additionally, some might argue that participation in potentially risky biomedical research is a "major life choice." Lawrence et al., *supra* note 1, at 216.

[65] *See* Smilan, *The Off-Label Loophole*, *supra* note 19, at 267 n.181, 268. The Author recognizes that there is great variability in mental illnesses and their treatment. While one medication, e.g., an antipsychotic, might alter the true self of the non-psychotic patient, that same medication may restore the true self of someone experiencing a "psychotic break" associated with bipolar disorder. *See id.* at 294.

[66] *See* Fortuna, *supra* note 15, at 579.

[67] *See* Corinne Lajoie et al., *Lived Experiences of Participation in Mental Health Research in Canada: Breaking the Glass Wall*, DISABILITY & SOCIETY, Oct. 14, 2020, at 13, 18 [hereinafter Lajoie et al., *Lived Experiences*], https://www.tandfonline.com/doi/abs/10.1080/09687599.2020.1833313 [https://perma.cc/5JNK-Z9H7] (describing how mental health research participants expressed that their participation fostered a sense of involvement and belonging in society, making them feel "important, valued, and listened to," believed, recognized, and helpful). Such recognition and validation "is especially meaningful for individuals who have historically been ignored and silenced." *Id.* at 14.

[68] Roberts, *supra* note 21, at 709.

[69] RESNIK, *supra* note 35, at 228 (citing NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 31, at iv; COUNCIL FOR INT'L ORG. OF MED. SCIS., INTERNATIONAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (3d ed. 2002); COUNCIL FOR INT'L ORG. OF MED. SCIS., INTERNATIONAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (4th ed. 2016)). Symptoms associated with mental illnesses can give rise to an ethical quandary for the psychiatrist who "wants to support the patient's ability to make an authentic autonomous choice [but questions] the stability of that choice." Lawrence et al., *supra* note 1, at 216.

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group membership, "but by characteristics unique to that person."[70] Another body of literature questions whether people suffering from mental illness need *any* protection against *their own* potential decision-making deficiencies.[71] In all the above examples, the myopic emphasis on potential participants lacking or possessing decision-making capacity—and the narrow definition of decision-making capacity and common beliefs about its assessment in people with mental illness—ignores all other sources of vulnerability to coercion or undue influence in this population. Traditional decision-making ability may appear intact, but may be affected by other vulnerabilities to coercion or undue influence, including the mental illness, the influences of psychotropic drugs, and imbalances in power dynamics experienced between the patient-participant and psychiatrist-researcher.[72] These factors may go completely unrecognized in the widely accepted assessment of decision-making capacity in research, the MacCAT-CR.[73]

The rCR leaves open how people with mental illness should be viewed in the

[70] Michelle Biros, *Capacity, Vulnerability, and Informed Consent for Research*, 46 J.L. MED. & ETHICS 72, 73 (2018).

[71] *See, e.g.*, Melissa D. McCradden & Michael D. Cusimano, *Questioning Assumptions About Vulnerability in Psychiatric Patients*, 9 AM. J. BIOETHICS NEUROSCIENCE 221, 222 (2018) ("Highlighting the vulnerability of patients with psychiatric disorders should not result in limiting their ability to participate in research."); Şerife Tekin, *Listening to Patients: A Pillar for the Epistemology of Neurointerventions*, 9 AM. J. BIOETHICS NEUROSCIENCE 239, 239 (2018) (there is a "gross and paternalistic overgeneralization that individuals with depression or other mental illnesses lack the capacity to make rational decisions."). But, arguing that those suffering from mental illness should have autonomy to make their own decisions "may [be] unintentionally undermin[ing], rather than protect[ing], the rights of seriously mentally ill patients" who lack autonomy because they cannot safely make treatment decisions "yet are often required, allowed, or left to do so." Arthur R. Williams, *Opportunities in Reform: Bioethics and Mental Health Ethics*, 30 BIOETHICS 221, 223 (2016). Williams states that "[a] philosopher's conception of an autonomous patient is predicated upon his or her own experience of reality. The absence of such perspectives within the field of bioethics undermines its ability to fully engage related content." *Id.* at 224. We are not doing psychiatric patients any favors by respecting their autonomy in situations where mental illness is stripping them of the ability to truly act autonomously. Fields & Calvert, *supra* note 50, at 469 ("[T]he boundary between autonomy and patient protection becomes blurred when patients do not have the capacity to make informed decisions."). This concern for patients translates to the clinical research setting as well. However, another argument weighing in favor of including potentially "vulnerable" subjects is that "[p]olicies that exclude individuals from research to protect them from harm, exploitation, or coercion/undue influence may adversely impact the health of the group to which they belong." RESNIK, *supra* note 35, at 233 (citing Anna Mastroianni & Jeffrey Kahn, *Swinging on the Pendulum: Shifting Views of Justice on Human Subjects Research*, 31 HASTINGS CTR. REP. 21, 25 (2001); DAVID RESNIK, THE PRICE OF TRUTH: HOW MONEY AFFECTS THE NORMS OF SCIENCE (2007)). Noteworthy is how in one qualitative study examining patient-participant perspectives on deep brain stimulation (DBS), where no pressure was placed to accept the intervention, patients were cautious despite their depressive symptoms and frustration with existing treatments. Lawrence et al., *supra* note 1, at 216. Chronically depressed subjects in this qualitative study were aware of their impaired decisionmaking abilities and would have elected to defer any decisions regarding undergoing DBS until they were feeling more stable. *Id.* Roberts posits, however, that "[s]uffering and pain due to . . . mental health problems may cause one to move toward a decision out of desperation rather than deliberateness and adherence to personal values and previous life choices." Roberts, *supra* note 21, at 706.

[72] *See* Laura Weiss Roberts et al., *Perspectives of Patients with Schizophrenia and Psychiatrists Regarding Ethically Important Aspects of Research Participation*, 157 AM. J. PSYCHIATRY 67, 68 (2000). "[T]he nature and quality of the investigator-participant relationship may greatly influence informed consent decisions of individuals with mental illness." *Id.* Roberts et al. noted that psychiatric patients were more accepting than psychiatrists of "the influence of physician investigators, personal physicians, and family members" on a patient's decision to participate in research. *Id.* at 71. Yet, "psychiatrists showed much stronger support than did our participants with schizophrenia regarding the inclusion of what have been defined historically as potentially vulnerable groups." *Id.* at 72. *See also*, Lajoie et al., *Lived Experiences*, *supra* note 67, at 13 (alteration in original) (quoting a mental health research participant's concerns about coercion and abuse in mental health research, stating that "the first time that [someone that has never been offered acceptation, tools, and support is recognized] as a human being, they're willing to buy into everything [the person listening to them] says or does.").

[73] *See, e.g.*, APPELBAUM & GRISSO, *supra* note 11, at 1-2.

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context of vulnerability to coercion or undue influence.[74] To cabin the mentally ill subject's vulnerability within traditional notions of decision-making capacity is short-sighted, though it is the trend in both the literature and in practice.[75] The rule's indecisiveness, however, provides an opportunity to expand protections and finally close the gaps originally identified by NBAC.[76] Suggested solutions on how to accomplish this are set forth later in this Article.

III. WHAT IS VULNERABILITY TO COERCION OR UNDUE INFLUENCE, AND WHO IS VULNERABLE IN THIS CONTEXT?

A. COMMON DEFINITIONS

"Coercion" and "undue influence" find their origins in the law.[77] The concept of "vulnerability," however, is rooted much more in ethics and social sciences than in law.[78] The Common Rule and the rCR do not define any of these terms,[79] but reaching a clear understanding of their meanings and implications in biomedical research is essential. Yet, many IRBs appear to use the terms "coercion" and "undue influence" interchangeably, without differentiation.[80] It has been argued that monitoring traditional notions of overt "coercion" and "undue influence" in research is insufficient, because other factors—social, cultural, economic, and political realities—may make research participation less voluntary and more a necessity.[81]

1. Coercion and undue influence in relation to mental illness

Though "coercion" and "undue influence" are undefined in the Common Rule and rCR, on its website, HHS discusses the need for investigators to avoid engaging in coercion and undue influence.[82] Coercion is described as follows:

> **Coercion** occurs when an overt or implicit threat of harm is intentionally presented by one person to another in order to obtain compliance. For example, an

[74] *See supra* notes 45-47 and accompanying text.

[75] *See, e.g.*, Fisher, *supra* note 11, at 74; *supra* note 52 and accompanying text.

[76] *See* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 31, at 53 (making recommendations related to review bodies, research design, informed consent and capacity, categories of research, surrogate decision-making, and education, research, and support).

[77] *See Coercion*, BLACK'S LAW DICTIONARY (11th ed. 2019) ("Compulsion of a free agent by physical, moral, or economic force or threat of physical force."); *Undue Influence*, BLACK'S LAW DICTIONARY (11th ed. 2019) ("The improper use of power or trust in a way that deprives a person of free will and substitutes another's objective; the exercise of enough control over another person that a questioned act by this person would not have otherwise been performed, the person's free agency having been overmastered.").

[78] The words "vulnerable" and "vulnerability" are not found in the widely accepted authority on legal definitions, Black's Law Dictionary. *See* BLACK'S LAW DICTIONARY (11th ed. 2019) (failing to include "vulnerable" or "vulnerability").

[79] *See* Common Rule, 45 C.F.R. § 46.102 (1991); Revised Common Rule, 45 C.F.R., § 46.102 (2019).

[80] Robert Klitzman, *How IRBs View and Make Decisions About Coercion and Undue Influence*, 39 J. MED. ETHICS 224, 226 (2013); *see also*, Jill A. Fisher, *Expanding the Frame of "Voluntariness" in Informed Consent: Structural Coercion and the Power of Social and Economic Context*, 23 KENNEDY INST. ETHICS J. 355, 370 n.4 (2013).

[81] Fisher, *supra* note 80, at 369.

[82] *See Informed Consent FAQs*, OFF. FOR HUM. RES. PROTECTIONS, U.S. DEP'T HEALTH & HUM. SERVS., https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html [https://perma.cc/QKG 2-T43X].

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> investigator might tell a prospective subject that he or she will lose access to needed health services if he or she does not participate in the research.[83]

Professor Jill Fisher asserts that limiting the concept of coercion to intentional acts fails to address the societal factors that force individuals to make choices they might otherwise not, absent their adverse circumstances.[84] The concept is described as "structural coercion" that has the potential to undermine the propriety of enrolling certain subjects in research.[85] Presented in the context of a person becoming a research participant out of desperation for a cure, for the purpose of obtaining money, or accessing general health care, the idea of "structural coercion" easily relates to psychiatric patients in research. Structural coercion takes into account that "broader power dynamics" outside the researcher-subject relationship "might infringe on the voluntariness of consent"[86] and prospective research participants might actually "turn to research in order to mitigate the threat of structural violence."[87] Again, Fisher presents structural coercion in the context of monetary incentives for participation, or participation to obtain basic health care or a miraculous cure, exploring the space where societal inequalities may limit opportunities and choices for potential research participants.[88] In this setting, there is something tangible, e.g., money, health care or experimental "treatment," that the participant lacks and desperately needs.[89] Structural coercion aptly applies to people who live with mental illness, a population that experiences housing insecurity, underemployment and unemployment, and insufficient treatment options.[90] In the case of the psychiatric patient-participant, beyond a need for sources of income, mental health care and treatments, reasons for participating in research might include a sense of belonging to something, a yearning for human interaction, and even feelings of friendship (e.g., with study staff)[91] after years of social isolation.

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[83] *Id.* This is consistent with the legal definition: Coercion "may be actual, direct, or positive, as where physical force is used to compel act against one's will, or implied, legal or constructive, as where one party is constrained by subjugation to other to do what his free will would refuse" and in the context of criminal law, coercion "can be mental as well as physical." *Coercion*, BLACK'S LAW DICTIONARY (5th ed. 1979). Note that the Belmont Report, the 1979 report by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, describes that coercion is present in instances where "an overt threat of harm is intentionally presented by one person to another in order to obtain compliance" and does not discuss implicit threats. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23, 192, 23,195 (Apr. 18, 1979).

[84] *See* Fisher, *supra* note 80, at 363-64.

[85] *Id.* at 360.

[86] *Id.* at 359.

[87] *Id.* at 360.

[88] *Id.* at 363-64.

[89] *See id.* at 365 (noting how Phase I investigational drug studies often pay thousands of dollars to participants, who view the money as a way to support themselves and their families)..

[90] *See* Fisher, *supra* note 80, at 364 ("What is often characterized by researchers and ethics scholars as participants' 'desperation' can influence people's perspectives that a clinical study is their only chance for an effective therapy or needed income."); *see also* Lajoie et al., *Lived Experiences*, *supra* note 67, at 6, 8 (describing testimony of one mental health research participant who explained that "participating in research studies helped her financially and made her feel helpful to society," and another who expressed that the financial compensation contributed to her decision to participate in research, along with the belief that participation would help her by getting her "mind off other things," in addition to making her feel valued and important).

[91] This brings to mind the friendship and sense of community at Miss Rivers' Lodge, where the nurse who played a central role in the Tuskegee syphilis study continued friendships with study subjects for decades. *See* Susan M. Reverby, *Rethinking the Tuskegee Syphilis Study: Nurse Rivers, Silence and the Meaning of Treatment*, 7 NURSING HIST. REV. 3, 18 (1999).

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HHS describes "undue influence" as arising in the context of inappropriate rewards, but also as present in other instances in more subtle form.[92] For example, HHS notes that where undue influence depends on a specific individual's situation, "it is often difficult for IRBs to draw a bright line delimiting undue influence" and that the IRB must "use its discretion in determining which circumstances give rise to undue influence."[93] This task becomes difficult because IRBs in most circumstances do not evaluate a particular participant's vulnerability to undue influence, and influence or "justifiable persuasion" is not per se unacceptable in research enrollment.[94]

The power imbalance between the patient-participant and psychiatrist-researcher may *unduly* influence a participant's choices.[95] This possibility is not surprising, as common sense suggests that the psychiatrist holds sway over the patient's decisions about psychiatric interventions.[96] For example, a participant in a qualitative study eliciting opinions from psychiatric patients about deep brain stimulation ("DBS") testified: "I have a psychiatrist who I have been with for a long time who has been prescribing medications for me and treating me and, now if he were to advocate for [DBS], and he had good reasons, that would be more persuasive."[97] This type of trust and deference can be expected to exist in most psychiatric clinician-patient and researcher-subject relationships, implicating concerns about voluntarism in consent.[98] Moreover, some scholars suggest an additional vulnerability: the distrust those suffering from mental illness often have in themselves.[99] True autonomy is hindered "when agents 'doubt their own worth and ability

[92] OFF. FOR HUM. RES. PROTECTIONS, U.S. DEP'T HEALTH & HUM. SERVS., *supra* note 82. The Belmont Report describes "undue influence" as such: undue influence "occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable. … [I]t is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threating to withdraw health services to which an individual would otherwise be entitled." Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192, 23,195 (Apr. 18, 1979). It logically would follow that manipulating a person's choice through the controlling influence of the psychiatrist-researcher on the patient-subject would likewise be an undue influence. This should be an expected possibility in the context of research with psychiatric patients.

[93] OFF. FOR HUM. RES. PROTECTIONS, U.S. DEP'T HEALTH & HUM. SERVS., *supra* note 82. "Undue influence" has been defined as: "Any improper or wrongful constraint, machination, or urgency of persuasion whereby the will of a person is overpowered and he is induced to do or forbear an act which he would not do or would do if left to act freely. Influence which deprives person influenced of free agency or destroys freedom of his will and renders it more the will of another than his own. Misuse of position of confidence or taking advantage of a person's weakness, infirmity, or distress to change improperly that person's actions or decisions." *Undue Influence*, BLACK'S LAW DICTIONARY (5th ed. 1979).

[94] *See* Fisher, *supra* note 80, at 357.

[95] Dearbhail Bracken-Roche et al., *The Concept of 'Vulnerability' in Research Ethics: An In-Depth Analysis of Policies and Guidelines*, 15 HEALTH RES. POL'Y & SYS., no. 8, 2017, at 16; *see also*, Nugent et al., *supra* note 18, at 444 ("We would hypothesize that mood disorders may make potential research participants perceive non-coercive external forces (for instance, a doctor's non-threatening recommendation) as influential in a way that is difficult to resist (due to, for example, loss of confidence in one's own opinions if they differ from those of a trusted authority figure's).").

[96] *See* Nugent et al., *supra* note 18, at 444.

[97] Lawrence et al., *supra* note 1, at 214.

[98] *See supra* note 71 and accompanying text (discussing voluntarism); *infra* note 157 and accompanying text (discussing "autonomous consent"); *see also* Roberts, *supra* note 21, at 706.

[99] Hannah Skye Martens & Timothy Emmanuel Brown, *Trusting Oneself and Others: Relational Vulnerability and DBS for Depression*, 9 AM. J. BIOETHICS NEUROSCIENCE 226, 227 (2018) (noting that in order to be complete, scholars' analyses of relationship vulnerability should consider one's relationship to oneself).

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to make appropriate choices.'"[100] Without considering this additional aspect of vulnerability—a lack of self-worth and self-trust—studies on how to counteract vulnerabilities of mentally ill participants will be incomplete and inherently flawed.[101]

Other less recognized sources of undue influence include the influence of psychotropic medications and changes in personality and preferences due to mental illness.[102] While mental illness or psychotropic medication may not change participants' decision-making ability, they may change the *decision* they make.[103] This scenario continues to be ignored under federal regulations designed to protect vulnerable people in human subjects research.

2. Vulnerability in relation to mental illness

The Common Rule and rCR point to "a vulnerable category" or "a category of subjects that is vulnerable to coercion or undue influence," respectively, in three contexts: (1) IRB membership,[104] (2) equitable subject selection,[105] and (3) the potential need for additional safeguards in research involving vulnerable subjects.[106] Overall, the Common Rule did little to define vulnerability; instead, it "convey[ed] a consent-based conceptualization of vulnerability that lack[ed] internal clarity regarding its scope."[107] This uncertain scope of vulnerability and the consent-based focus on decision-making capacity continue under the rCR.[108]

For years scholars have attempted to forge meaning where little or no guidance exists.[109] The result is a disorganized, minimally useful literature focused on

[100] *Id.* (quoting Carolyn McLeod & Susan Sherwin, *Relational Autonomy, Self-Trust, and Health Care for Patients Who are Oppressed*, *in* RELATIONAL AUTONOMY: FEMINIST PERSPECTIVES ON AUTONOMY, AGENCY, AND THE SOCIAL SELF 259, 262 (Catriona MacKenzie & Natalie Stoljar eds., 2000) (citation omitted)).

[101] *Id.*

[102] *See* Smilan, *supra* note 19, at 303-04 (noting that psychotropic medications sedate and control patient behaviors, often with "life-altering chronic and irreversible side effects"). Nugent et al. note that "[i]nformed consent requires that decisional autonomy not be compromised by either external and potentially coercive forces, or by *internal forces* resulting from the illness or impairment." Nugent et al., *supra* note 18, at 444 (emphasis added).

[103] *See* Elliott, *supra* note 7, at 114 (noting that an actor's emotional state may impair his decision-making and render him incompetent to consent to treatment).

[104] Revised Common Rule, 45 C.F.R. § 46.107 (2019) (recommending inclusion of persons who are knowledgeable about and experienced in working with vulnerable subjects); Common Rule, 45 C.F.R. § 46.107 (1991).

[105] 45 C.F.R. § 46.111(a)(3) (2019) (advising researchers to account for the purpose and setting of the research when selecting subjects); 45 C.F.R. § 46.111(a)(3) (1991).

[106] 45 C.F.R. § 46.111(b) (2019) (requiring additional safeguards for vulnerable subjects); 45 C.F.R. § 46.111(b); *see* Hurley, *supra* note 48 (noting that beyond the circumstances of enrollment, also important is how subjects are treated throughout the research process).

[107] Bracken-Roche et al., *supra* note 95, at 15.

[108] *See* Hurley, *supra* note 48 (noting that exploitation, excessive risks, and exclusion are types of vulnerability in research beyond coercion and undue influence). If anything, language in the rCR seems to yield even more discretion to IRB members than did the original rule by requiring judgments on the scope and parameters of "impaired decision-making capacity," with no direction on implementation. *See* 45 C.F.R. § 46 (2019) (requiring special protections for persons with "impaired decision-making capacity" without defining this term).

[109] *See, e.g.*, Eric Racine & Dearbhail Bracken-Roche, *Enriching the Concept of Vulnerability in Research Ethics: An Integrative and Functional Account*, 33 BIOETHICS 19, 20 (2018) (noting that scholars struggle to agree on consistent use and understanding of vulnerability in research ethics); Wendler, *supra* note 20, at 520 (defining "vulnerable" according to Merriam Webster's Dictionary, research literature, and standard English).

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vulnerability.[110] The dictionary defines a "vulnerable" person as one capable of being physically or emotionally wounded, or open to attack or damage.[111] Worldwide, policies and guidelines on clinical research ethics rarely define "vulnerability," but they generally "convey implicitly that vulnerability is fundamentally an inability to provide free and informed consent."[112] Some assert that "mental illness creates an inherent vulnerability,"[113] while others maintain that such a notion risks overinclusion and furtherance of stigmatization and discrimination.[114]

B. A Closer Look at the Origins of "Vulnerability"

Authored by the National Commission, the Belmont Report was the first official influential writing to identify vulnerability as a factor requiring significant attention in clinical research ethics.[115] The report states that one necessary consideration in assessing justifiability of research with humans is:

> (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.[116]

Under "Selection of Subjects," the report states that research targeting *particular groups* gives rise to injustice. [117] These groups include:

> racial minorities, the economically disadvantaged, the very sick, and the institutionalized . . . Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are

[110] Wendler, *supra* note 20, at 520 (citing Kenneth Kipnis, *The Limitations of* "Limitations", 4 AM. J. BIOETHICS 70, 70 (2004)); *see also* Racine & Bracken-Roche, *supra* note 109, at 20 ("[S]cholars have been advancing competing accounts of vulnerability and struggling to reach consensus about the conceptualization and operationalization of vulnerability in research ethics.").

[111] *Vulnerable*, MERRIAM WEBSTER DICTIONARY, https://www.merriam-webster.com/dictionary/vulnerable [https://perma.cc/Q3UB-VARA]. The words "vulnerable" and "vulnerability" do not appear in Black's Law Dictionary. BLACK'S LAW DICTIONARY (11th ed. 2019) (defining only "vulnerable adult," "vulnerable-adult abuse," and "vulnerable zone").

[112] Bracken-Roche et al., *supra* note 95, at 16.

[113] Lawrence et al., *supra* note 1, at 216 (citing Andrew Coulter, *Deep Brain Stimulation Research Protocols and Depressive Patients with Previous Suicidality: We Can't Afford to Lose Focus*, 4 AM. J. BIOETHICS NEUROSCIENCE 41, 41 (2013)).

[114] *See* Lajoie et al., *Concept of Vulnerability*, *supra* note 10, at 140 (citing the need for further qualitative research on mental health research participants' perspectives regarding vulnerability in mental health and views relating to possible overuse and stigmatization).

[115] Bracken-Roche et al., *supra* note 95, at 1; *see also* Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192, 23,195 (Apr. 18, 1979).

[116] Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. at 23,195.

[117] *Id.* at 23,196 ("Injustice may appear in the selection of subjects, [because] even if individual subjects are selected fairly . . . unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research.").

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> *easy to manipulate as a result of their illness* or socioeconomic condition.[118]

The National Commission recommended requiring additional protections in human subjects research involving pregnant women, fetuses, neonates, prisoners, children, and the *mentally infirm.*[119] While every other category was listed explicitly as a vulnerable population in the final Common Rule, the rule did not prescribe heightened protections for institutionalized "mentally infirm" subjects due to "concern that [such protections] might block valuable and appropriate research."[120] In its final 1991 iteration, the Common Rule mentioned subjects "'likely to be vulnerable to coercion or undue influence,' including mentally disabled persons,"[121] but, as noted above, did not define mental disability.[122]

Since publication of the Belmont Report, legal and nonlegal policies and guidelines relating to clinical research ethics have expanded worldwide; along with this expansion, the meanings and conceptual scopes of vulnerability and vulnerable populations have branched in nuanced directions.[123] Scholars have put forth various interpretations. For example, one analysis suggests that vulnerability is an "additional susceptibility to research-related harm or risk, or that additional safeguards are needed to

[118] *Id.* at 23,197 (emphasis added).

[119] Wendler, *supra* note 20, at 517; *see also* Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. at 23,196.

[120] Wendler, *supra* note 20, at 517 (citations omitted); *see also* Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled, 43 Fed. Reg. 53,950, 53,950 (proposed Nov. 17, 1978) (to be codified at 45 C.F.R. pt. 46) ("[Institutionalized mentally infirm] persons by the very nature of their disabilities may not be competent to provide informed consent . . . . At the same time, the nature of their disabilities requires extensive research efforts to study the etiology, pathogenesis, prevention, therapy, and management of their conditions."). This "justification" for excluding mentally ill people from heightened protections while imposing unnecessary restrictions on pregnant women is illogical if it was done in good faith, and makes perfect sense if done to perpetuate stereotypes and inequitable gender roles in the case of pregnant women and make research with mentally ill patients who lacked the wherewithal to protect themselves that much easier for researchers.

[121] Wendler, *supra* note 20, at 517. Similarly, FDA regulations regarding criteria for IRB approval of research in the context of clinical research, state: "When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects." 21 C.F.R. § 56.111(b) (2001); *see also* 21 C.F.R. § 56.111(a)(3) (2001) (stating that the IRB should be cognizant of the special research problems encountered by vulnerable populations); 21 C.F.R. § 56.107(a) (1991) (requiring at least one IRB member be "primarily concerned" with the welfare of vulnerable subjects if the IRB regularly reviews research involving these populations). FDA's regulations have not been modified by the rCR.

[122] Left to the interpretations of IRB members, "mentally disabled" persons could be those suffering from brain damage, or those with congenital brain abnormalities, or those with physical ailments that affect brain functioning. *See* Hoffman et al., *supra* note 40, at 550 ("Federal regulations merely call on [IRBs] to be attentive to the need for 'additional safeguards' . . . ."). Likewise, the term could be interpreted to include those with medically diagnosed mood disorders. *See* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 31, at 1-2, 5 (finding that "mental disorders," including mood disorders such as depression, cannot be precisely defined, yet the condition may still affect the person's ability to give informed consent and should thus qualify persons with mental disorders for special IRB protections as vulnerable populations during moments of impairment). Outcomes of IRB determinations could thus be driven entirely by who was sitting at the IRB table that particular day at that particular research institution. *See* Justin T. Clapp et al., *Justification and Authority in Institutional Review Board Decision Letters*, SOC. SCI. & MED., Dec. 2017, at 25, 28 (finding "substantial qualitative variation in . . . thoroughness and apparent clarity" when examining IRB rationales for stipulating changes to proposed studies).

[123] Bracken-Roche et al., *supra* note 95, at 1.

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protect the potential participant from research-related risk or harm."[124] Another approach imagines layers of vulnerability "which arise from interactions between an individual's characteristics and their environment, and which interact with one another to create an inextricably context-dependent vulnerability."[125]

One of the more influential interpretations of vulnerability in human research divides vulnerability into six subcategories: "cognitive, juridic, deferential, medical, allocational, and infrastructural."[126] Categories most relevant to people suffering from mental illness are cognitive vulnerability and deferential vulnerability.[127] Cognitive vulnerability that impairs decision-making capacity may be either permanent, as with Alzheimer's disease or brain injury, or temporary, e.g., an episode of major depressive disorder.[128] Deferential vulnerability highlights that an individual could possess cognitive decision-making capacity but still be influenced by others' opinions "such that they are not able to decide based on their own preferences and values."[129] A power imbalance between the researcher and a subject suffering from mental illness could serve as fertile ground for deferential vulnerability.[130] In fact, scholarly literature acknowledges "that vulnerability is a relational feature, borne of power asymmetries between participants and research staff, investigators and institutions."[131]

Another conception of vulnerability asserts that *all* research subjects are vulnerable; this conception should be challenged, then dismissed.[132] The notion of universal vulnerability in clinical research—which can be described as a "categorical claim" of vulnerability—is "both clearly right and fundamentally problematic."[133] While all human beings are susceptible to harm, ascribing vulnerability to all human subjects serves to "undermine rather than promote" protections for clinical research subjects.[134] Such a generalized definition supports the need for research regulation in general,[135] but if we insist on employing "special protections" for all subjects, then we are "providing special protections for no one."[136] It is argued, however, that attempts to formulate specific lists of vulnerable populations can lead to stigmatization and the harmful suggestion that

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[124] Biros, *supra* note 70, at 75 (citing Jo Aldridge, *Working with Vulnerable Groups in Social Research: Dilemmas by Default and Design*, 14 QUALITATIVE RES. 112, 113 (2014)); *see also*, Bracken-Roche et al., *supra* note 95, at 2 (citing Samia A. Hurst, *Vulnerability in Research and Health Care; Describing the Elephant in the Room?*, 22 BIOETHICS 191, 195 (2008)).

[125] Bracken-Roche et al., *supra* note 95, at 2 (citing Florence Luna & Sheryl Vanderpoel, *Not the Usual Suspects: Addressing Layers of Vulnerability*, 27 BIOETHICS 325, 326 (2013)).

[126] Wendler, *supra* note 20, at 517.

[127] CARL H. COLEMAN ET AL., THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS 141-43 (2d ed. 2015) (citing 1 NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL & POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 88-89 (2001)).

[128] Fields & Calvert, *supra* note 50, at 463-64; *see also* MacFarlane et al., *supra* note 50, at 64 (explaining temporary impairments and listing examples of such transient impairments).

[129] Wendler, *supra* note 20, at 517. Interestingly, in a recent qualitative study, one participant living with mental illness stated that "you lose your capacity to make decisions in a sense. No, not your capacity, but it makes it harder […]. [You're] quite vulnerable to whatever doctors will tell you you should do or your parents or your family or husband, whatever." Lajoie et al., *Enriching our Understanding*, *supra* note 24, at 451.

[130] *See* Bracken-Roche et al., *supra* note 95, at 16 (noting the capability of research environments to disempower research participants and subjects).

[131] *Id.* at 16.

[132] Wendler, *supra* note 20, at 519 (citing Frederick Grinnell, *Subject Vulnerability: The Precautionary Principle of Human Research*, 4 AM. J. BIOETHICS 72, 73 (2004)) (recognizing that all humans are vulnerable before challenging the claim and concluding that vulnerability in clinical research is comparative and context dependent).

[133] *Id.* at 519, 522.

[134] *Id.* at 519.

[135] *Id.* at 524.

[136] *Id.* at 516.

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persons on these lists are "everywhere and always" incapable of taking care of themselves and their interests.[137] The Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans ("TCPS2") states that "*individuals should not automatically be considered vulnerable simply because of assumptions made about the vulnerability of the group to which they belong*."[138]

Lists and categories may strip individuals of autonomy not only in the research setting, but in other areas of life as well.[139] While categories may be problematic, so too is the current "IRB free-for-all" in interpreting U.S. federal regulations[140] as they relate to people who suffer from mental illness.[141] Without lists, firm definitions, or guidance, a category of subjects may be deemed "vulnerable to coercion or undue influence" at one institution on a given day and "not vulnerable to coercion or undue influence" at another institution, or even the same institution, the very next. Erring on the side of more protections may be better than insufficient and inconsistent protections.[142] Requiring consideration of heightened protections should not stymie research with mentally ill participants, but should aim to add structure and consistency to the research endeavor so those who might need extra protections are afforded them.

To counter the risk for "over-inclusiveness" in describing people who require additional protections in research, some scholars rely on comparative and contextual analyses.[143] A comparative approach to defining vulnerability highlights that protections needed for a particular subclass may be more than are necessary for the class as a whole.[144] A contextual analysis additionally contemplates under what circumstances this particular subclass requires additional protections.[145] Another relevant consideration is "situational" vulnerability, which involves temporary vulnerability.[146]

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[137] *Id.*; *see also* Morian-Sanchez, Luna & Perez-Carceles, *supra* note 50, at 102.

[138] Bracken-Roche et al., *supra* note 95, at 10 (quoting CAN. INST. OF HEALTH RESEARCH, NAT. SCIS. AND ENG'G RESEARCH COUNCIL OF CAN., & SOC. SCIS. AND HUMANITIES RESEARCH COUNCIL OF CAN., TRI-COUNCIL POLICY STATEMENT: ETHICAL CONDUCT FOR RESEARCH INVOLVING HUMANS 54 (2014) (Can.)). Here one can see the merit of arguments against naming all people with mental illness as vulnerable to coercion or undue influence.

[139] DuBois et al., *supra* note 8, at 2222, 2224. "Labeling particular groups as at risk for lacking decisional capacity or as incapable of making a voluntary choice reinforces stigma or stereotypes, when in fact members of such groups are frequently diverse and function as well as so-called healthy volunteers." *Id.* at 2222 (citations omitted).

[140] Leaving some discretion to ethics oversight committees or IRBs is often a good thing; however, inconsistent practices among various research institutions receiving federal funding is indeed problematic.

[141] MacFarlane et al., *supra* note 50, at 64; *see also* Racine & Bracken-Roche, *supra* note 109, at 20 (discussing research ethics boards in Canada, a similar challenge there "of assessing and appropriately responding to vulnerability," and implications for potentially vulnerable research subjects that may flow from boards' actions or inaction); Yanos et al., *supra* note 50, at 374 (recognizing the lack of consensus among IRBs "on how to evaluate studies in which considerations of both degree of risk and vulnerability need to be made").

[142] Though, some scholars complain that "IRB members overestimate the risk of incapacity" present in the psychiatric patient population while underestimating levels of risk for patients with medical diagnoses that are unrelated to mental illness but nonetheless may impair decisional capacity. DuBois et al., *supra* note 8, at 2222 (citing Luebbert et al., *IRB Member Judgments of Decisional Capacity, Coercion, and Risk in Medical and Psychiatric Studies*, 3 J. EMPIRICAL RES. ON HUM. RES. ETHICS 15, 15 (2008)).

[143] Wendler, *supra* note 20, at 516.

[144] *Id.* at 522.

[145] *Id.* at 524 (recognizing how a contextual analysis may determine "that only some subjects are vulnerable" and "whether there are individuals for whom the general protections are not sufficient").

[146] Biros, *supra* note 70, at 75.

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C. VOLUNTARISM MUST BE CONSIDERED IN ASSESSING MENTALLY ILL PARTICIPANTS' VULNERABILITIES TO "COERCION OR UNDUE INFLUENCE"

Bioethicists have conjured numerous interpretations and conceptions of what it means to be vulnerable, which makes it all the more remarkable that most interpretations of the Common Rule and rCR employ impaired decision-making capacity [147] as the sole criterion for determining mentally ill participants' vulnerability to coercion or undue influence.[148] Again, while specifically naming persons who are vulnerable—prisoners, children, educationally or economically disadvantaged individuals, as well as individuals with impaired decision-making capacity—the introductory language "such as" clearly leaves the field open.[149] Impaired decision-making capacity is but one example of vulnerability to coercion or undue influence:[150] whether or not this was the intent of those who drafted the rCR, the words "such as" are akin to the legalese "including but not limited to."

Asserted earlier in the Article, the need for additional protections for participants suffering from mental illness may not necessarily arise from an impairment in decision-making ability, but rather from a sometimes undetectable susceptibility to coercion or undue influence from a variety of sources.[151] For these individuals, the effects of mental illness, psychotropic medications, power dynamics, and "structural coercion"[152] may not alter their ability to make *a* decision, but can change *the decision they make*.[153] The rCR ignores this possibility, not necessarily as written but as interpreted and applied in practice.

This type of susceptibility—the risk of *altered* decision-making—is the very type of situation where the concept of "voluntarism" is implicated.[154] Professor Laura Weiss Roberts asserts that informed consent has three components: information, decisional capacity, and voluntarism.[155] Voluntarism is "the individual's ability to act in accordance with one's authentic sense of what is good, right, and best in light of one's situation, values, and prior history," and "involves the capacity to make [choices] freely and in the absence of coercion."[156] Unfortunately, voluntarism is often overlooked, if considered at all.[157] Instances may arise where, for example, mental illness or psychotropic medications unduly influence thought processes, preferences, and judgments and may, in fact, alter the patient's decision to participate in clinical research.[158] Under these circumstances, choices may not be truly voluntary because they do not reflect the

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[147] There are many instances that might give rise to impaired decision-making capacity: One might include a person in a comatose state after an automobile accident, another a person experiencing catatonia due to disease or infection. The category "impaired decision-making capacity" includes many potential research subjects, diluting the specific needs of and attention given those who are suffering from mental illness. *See, e.g.*, RESNICK, *supra* note 35, at 217-20.

[148] *See generally id.* at 217-19 (summarizing different bioethicist's definitions of vulnerable populations).

[149] *See supra* Section II.C.

[150] *See* RESNICK, *supra* note 35, at 217-19 (recognizing the vagueness of the Common Rule and the term "vulnerability" in summarizing a non-exhaustive list of vulnerable populations).

[151] *See supra* Section II.D.

[152] Fisher, *supra* note 80, at 360.

[153] *See* Elliott, *supra* note 7, at 114.

[154] *See* Roberts, *supra* note 21, at 705.

[155] *Id.*

[156] *Id.* at 707.

[157] *See* Smilan & Conklin, *supra* note 64, at 33-34 (using the term "autonomous consent" to highlight how true autonomy may be lacking in consent where the effects and implications of mental illness make voluntarism—a necessary component of autonomous consent—unlikely or impossible).

[158] *See* Elliot, *supra* note 7, at 114-15.

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participant's true self.[159] Due to these concerns, the concept of voluntarism should be a key factor in determining a mentally ill participant's vulnerability to coercion or undue influence.

IV. CONSULTING THE EXPERTS

One scholar suggests that appropriate protections for research participants need not focus on the "concept of vulnerability" or involve attempts to create lists or categories of vulnerable populations.[160] Instead, this scholar argues that experts must develop guidelines to determine group and individual vulnerabilities based on the contexts of particular studies and certain circumstances, and *then* formulate context-specific protections.[161] This approach relies on "*expertise* regarding the specific individuals and contexts in question."[162] But, it raises obvious questions: How much representation of individual participants is feasible? What is meant by expertise? Who is an expert? Might expertise differ based on context? And finally, is the expert the psychiatrist or the psychiatric patient? To answer this last question, perhaps both individuals possess expertise that is complementary but not necessarily overlapping. Another source of expertise might be leaders at HHS, the National Institutes of Mental Health, and mental health advocacy groups.

A. THE EXPERIENCED RESEARCH PARTICIPANT

One novel proposal suggests that experienced research participants have expertise, and directly engaging them in conversation will better inform research ethics and oversight.[163] This approach recommends appointment of experienced research subjects to research ethics and policy development committees and IRBs.[164] Alternatively, institutions could establish advisory groups of research participants with varied experiences who could be called upon for specific issues by their human subjects protection programs.[165] More generally, it is asserted that engaging research participants with first-hand experiences is necessary to develop research ethics and policy and to strengthen the factual and moral bases of guidelines and regulations.[166]

Some challenges of this proposal are readily apparent. The recommendation of including research subjects as IRB members may be unrealistic for certain populations,

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[159] Earlier scholarship discussed the authenticity of a mentally ill person's actions and behaviors: "The authenticity argument supposes a person with a stable character and entrenched dispositions, who, while depressed, makes decisions so uncharacteristic that we feel bound to question whether those decisions were truly hers." *Id.* at 115. The Author acknowledges that for certain severe mental illnesses, e.g., schizophrenia, it is the psychotropic medication that may elicit the true self of the psychiatric patient. *See* Smilan, *supra* note 19, at 302; Thompson et al., *supra* note 19, at 161.

[160] Wendler, *supra* note 20, at 524.

[161] *Id.*

[162] *Id.* (emphasis added).

[163] Rebecca Dresser, *Experimentation Without Representation*, 40 IRB. 3, 5 (2018). Bracken-Roche and colleagues similarly suggest that research participants, who "seem to have been largely left out of the development of research ethics guidelines" might also be important to the process of framing vulnerability. Bracken-Roche et al., *supra* note 95, at 17.

[164] Dresser, *supra* note 163, at 5. Dresser acknowledges the inherent challenges in tasking research institutions and organizations with locating and recruiting research subjects as advisors or board members who also have "the necessary contacts and background to represent" the diversity and diverse experiences of other research participants. *Id.* at 6. In arguing for her proposed initiative, Dresser notes that "the complex perspectives of researchers, ethicists, and members of the public are weighed and balanced in research ethics and policy deliberations. Subjects' complex perspectives could simply be added to the mix." *Id.*

[165] *Id.* at 5.

[166] *Id.*

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such as those in studies on terminal diseases.[167] For these groups, an unfortunate but inevitable attrition rate would deplete the pool of individuals available to serve as IRB members. Participants in studies implicating stigmatized diseases—e.g., clinical trials for antidepressant drugs—could experience repercussions in their personal, social, and professional lives if it is somehow disclosed that they serve as a representative of those suffering from mental illness.[168] For someone carrying the burden of mental illness and trying to get well or maintain wellness, this may be too much to ask.

B. Representation Through Empirical Research

Another approach suggests accessing the expertise of veteran research participants less directly, relying on empirical research as the preferred method of including participants' views.[169] Built into this empirical research, however, is a power imbalance between researchers and participants.[170] With empirical studies that "express" the affected population's perspectives, the "research community remains in control of the research and continues to determine its appropriateness, and research participants remain outside of the room except for their indirect voices in the data."[171] This point warrants repeating: ethics research on clinical research subjects is framed and interpreted by researchers.[172] And inherent in research design are the "'value judgments' that necessarily reflect the background beliefs, the vested interests and the ideology of the investigator."[173]

Nonetheless, a recent qualitative study, hereafter "the Lawrence study," is a fine example of indirect representation through examining depressed patients' attitudes about DBS, an experimental intervention for treatment-resistant depression.[174] Psychiatry has a tempered hopefulness about the effectiveness of DBS, but optimism is based on inconsistent results seen in case reports and small open-label trials with no control groups.[175] The limited data on efficacy raises "ethical questions about vulnerability" in potential DBS patients.[176] Recognizing concern within the research community about unrealistic hopes, feelings of desperation, or inability to adequately weigh risks and benefits, the Lawrence study interviewed treatment-resistant depressed patients to assess

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[167] *See* Stephanie Solomon Cargill, *Moving from the "Why" to the "How": Two Approaches to Including Research Participants' Voices*, 40 IRB 8, 9 (2018).

[168] *See, e.g.*, Yokoya et al., *supra* note 22, at 203.

[169] Cargill, *supra* note 167, at 9. Cargill concedes that the indirect approach of research subject input via empirical research may be compromised by "the current dearth of empirical research on research ethics, and research with research participants in particular." *Id.* at 10. Also problematic is the difficulty in locating ethics research studies and translating mixed-methods or qualitative work into generalizable information. *Id.*

[170] *Id.*

[171] *Id*. Cargill states that this could result in strategic use of participant perspectives only "where it would promote the efficacy or expediency of research, and its dismissal in realms where it may hinder or challenge it." *Id.*

[172] *See id.*

[173] Abby Lippman, *Led (Astray) by Genetic Maps: The Cartography of the Human Genome and Health Care*, 35 SOC. SCI. & MED. 1469, 1472 (1992) (quoting Stuart F. Spicker & H. Tristram Englehardt, Jr., *Causes, Effects, and Side Effects: Choosing Between the Better and the Best*, *in* 16 PHILOSOPHY OF MED., HEALTH, DISEASE, AND CAUSAL EXPLANATIONS IN MEDICINE 225, 225 (Lennart Nordenfelt & B. Ingemar B. Lindahl eds., 1984)).

[174] Lawrence et al., *supra* note 1, at 210. "Deep brain stimulation is a neurosurgical procedure in which electrodes are placed inside the brain and an electrical current is delivered to specific brain regions." *Id.* While conducted with 24 adult psychiatric in-patients, excluded were patients "experiencing psychosis, delirium, dementia, intoxication, or catatonia, or [those with an] intellectual disability (mental retardation), . . . under court-ordered treatment, or [who] were non-English speaking." *Id.* at 212.

[175] *Id.* at 210.

[176] *Id.* at 211.

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"interest level, hopes, fears, and decision-making processes."[177] Study participants appeared to understand the risks of DBS, were aware of their own limitations in processing information, and expressed cautious approaches to considering engagement in clinical research trials.[178]

While qualitative studies often allow research participants opportunities for elaboration and originality of thought, the researcher devises the initial prompts.[179] Criticisms of the Lawrence study point out that the authors summarily and prematurely dismissed relational vulnerabilities, both "power-relational vulnerability"[180] and "identity-relational vulnerability."[181] It is also suggested that participants in the Lawrence study should have been asked additional questions to fully analyze relational vulnerabilities and avoid misleading conclusions.[182] Even so, first-person accounts of prospective research participants who suffer from mental illness, and evidence-based research focused on their experiences, undoubtedly are valuable sources of information for mental health research.[183]

C. Expertise on Institutional Review Boards

As shown in Part II, the rCR still requires consideration of including on IRBs those with knowledge about and experience *working with* subjects from potentially vulnerable categories.[184] IRB community members, however, can be quite seasoned by life experience or education, without having worked with a particular population. The rule's "working with" requirement is an unnecessary limitation. Further, while the rCR requires that every IRB have at least one community member,[185] providing the opportunity to recruit community members experienced with particular populations, little evidence demonstrates that IRB community members are assigned to reviews based on their specific knowledge or interests.[186]

It is possible to recruit and assemble a pool of IRB community members who have acquired expertise or highly relevant knowledge through various avenues, supplementary to or by means other than employment.[187] The discretionary mandate—effectively no mandate at all—that "consideration *shall be* given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects" is a missed opportunity to actually mandate or strongly encourage inclusion of the rich knowledge base accessible through targeted IRB community member

[177] *Id.* The cohort was not drawn from patients who had self-selected DBS as a potential treatment, but instead patients who were not necessarily seeking this treatment. *Id.*

[178] *Id.* at 217.

[179] *See* Loraine Busetto et al., *How to Use and Assess Qualitative Research Methods*, 2 NEUROLOGICAL RES. & PRAC., no 14, 2020, at 1, 2, 6 (explaining the researcher's ability to make educated decisions regarding methods and the importance of reflexivity).

[180] Boulicault & Brown, *supra* note 21, at 235 (citing Bell et al., *supra* note 62, at 364) (describing "power-relational vulnerability" as "the vulnerability a research participant experiences as a result of asymmetrical power relations existing between investigators and participants").

[181] *Id.* at 236 (describing "identity-relational vulnerability" as "vulnerability that arises from how a person's (evolving) self-identity both shapes and is shaped by their relationships with others").

[182] *Id.*

[183] Şerife Tekin, *supra* note 71, at 240.

[184] Revised Common Rule, 45 C.F.R. § 46.107 (2019).

[185] *Id.*

[186] *See* Robert Klitzman, *Institutional Review Board Community Members: Who Are They, What Do They Do, and Whom Do They Represent?*, 87 ACAD. MED. 975, 978-79 (2012) (finding that IRBs vary widely in the roles and functions assigned to community members).

[187] The "working with" requirement may exclude perspectives of community members who are disabled or not members of the traditional workforce. *See* 45 C.F.R. § 46.107 (2019).

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recruitment and assignment.[188]

V. POSSIBLE SOLUTIONS

A. WHAT HHS COULD/SHOULD DO

HHS must either further revise the rCR or issue binding guidance on biomedical research with people who suffer from mental illness. Three points should be kept in mind: (1) some who live with mental illness or conduct research with this community assert that "it is stigmatizing to equate a mental illness with incapacity,"[189] that "no one-to-one relationship between a psychiatric disorder and decisional incapacity" exists, [190] and that it is inappropriate to label all people with mental illness as vulnerable;[191] (2) as interpreted and applied in practice, decisional capacity is the exclusive mechanism under the rCR for viewing the vulnerabilities to coercion and undue influence in people with mental illness;[192] and (3) individuals with mental illness can be deemed to have traditional decision-making capacity based on widely accepted assessments, but still be vulnerable to coercion or undue influence for other reasons.[193] HHS does not need to amend rCR language to designate all people who suffer from mental illness as vulnerable. This approach would likely be met with substantial pushback from researchers,[194] community advocacy groups, and perhaps many individuals who live with mental illness. But, the current use of "such as . . . individuals with impaired decision-making capacity" creates a catch-all category for vulnerabilities to coercion or undue influence arising from mental illness that is simply too narrow.

A rather straightforward proposal would be to amend the rCR by adding a reference to "subjects who are *potentially vulnerable* to coercion or undue influence, such as individuals who suffer from mental illness" in both "Criteria for IRB Approval of Research" at 45 C.F.R. §§ 46.111(a)(3), (b) and "IRB Membership" at 45 C.F.R. § 46.107. The use of "potentially vulnerable" would likely satisfy legitimate objections to labeling all people with mental illness as vulnerable to coercion or undue influence. Saying people with mental illness are potentially vulnerable to coercion or undue influence is less essentialist and judgmental than saying they *are* vulnerable, always.

Alternatively, HHS could bypass any need for additional formal rulemaking, instead issuing binding guidance to clearly address and fill the enduring gaps in

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[188] *Id.* (emphasis added). This proposition is discussed more fully in Part IV. *See supra* Part IV.

[189] Jeste & Saks, *supra* note 19, at 623.

[190] *Id.* at 609.

[191] *See* Nugent et al., *supra* note 18, at 447; Lajoie et al., *Concept of Vulnerability*, *supra* note 10, at 129.

[192] *See supra* Sections II.C, II.D.

[193] *See supra* text accompanying note 52 and Section II.D.

[194] Nugent et al. state that it is potentially harmful to declare all adults with mood disorders to be a vulnerable population, potentially contributing to stigma and devaluing of the societal contributions made by people with mood disorders. Nugent et al., *supra* note 18, at 447. These scholars draw comparisons between the dying cancer patient who consents to risky research and the patient suffering from depression because "severely ill patients rate the state of severe depression as equivalent to or worse than death." *Id.* It is understandable why those who conduct research with mentally ill people want to show how their work is justifiable and should not be interfered with, however, there is no comparison between a dying cancer patient who literally has no alternative treatment and elects—with mental functioning fully intact—to take a huge risk to possibly avoid death and the severely depressed patient whose mental functioning is likely greatly compromised to take a huge risk in agreeing to take investigational psychotropic drugs or undergo other experimental psychiatric interventions. *See* Smilan, *supra* note 19, at 296-97.

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protections for mentally ill people in biomedical research.[195] First, HHS should provide definitions or guidance on the rCR's vague concepts, e.g., the parameters of being "vulnerable to coercion or undue influence." HHS should also answer whether it intended for IRBs to exclude all factors beyond traditional notions of decision-making capacity when considering how to properly protect mentally ill participants against vulnerabilities to coercion or undue influence: if that was the department's intent, this stance must be revisited. Without officially revising the regulation's language, binding guidance could offer clarifications. Additionally, effective guidance related to operationalizing the charge to IRBs under 45 C.F.R. § 46.111(b), that would facilitate needed protections for mentally ill participants, might look something like the proposed guidance set forth in *Figure 1*:

[195] Nugent et al. argue that our current system of informed consent is adequate, and that characteristics such as "extreme hopelessness and/or willingness to assume risk inappropriately should be relatively obvious in any properly conducted informed consent discussion, and could be deemed to invalidate consent." Nugent et al., *supra* note 18, at 446. Underlying studies, such as those examined by Nugent et al. (to support their conclusions), that consider the benefits of research with mentally ill people are problematic in that research that asks mentally ill people about their experiences with research must be eyed with some skepticism: Structural coercion (or regular coercion) and undue influence may have been factors affecting their choices and preferences for the original research in which they participated, and then similarly in the research about that research. *See, e.g.*, *id.* at 445-47; Monika Edlinger et al., *Attitudes of Patients with Schizophrenia and Depression Towards Psychiatric Research*, 177 PSYCHIATRY RES. 172 (2010); Sashana Misra et al., *Appreciation of Research Information in Patients with Bipolar Disorder*, 10 BIPOLAR DISORDERS 635 (2008); Laura Weiss Roberts & Jane Paik Kim, *Giving Voice to Study Volunteers: Comparing Views of Mentally Ill, Physically Ill, and Healthy Protocol Participants on Ethical Aspects of Clinical Research*, 56 J. PSYCHIATRY RES. 90 (2014); Deborah Tallon et al., *Involving Patients with Depression in Research: Survey of Patients' Attitudes to Participation*, 61 BRIT. J. GEN. PRAC. 134 (2011); Cathy Spatz Widom & Sally J. Czaja, *Reactions to Research Participation in Vulnerable Subgroups*, 12 ACCOUNTABILITY IN RES. 115 (2005); *see also* Fisher, *supra* note 80, at 360 (introducing the concept of structural coercion). Nugent et al. use as an example one study of participants experiencing active mental distress associated with adult and childhood trauma, stating that these participants "were even more likely to state that they would participate in research again than those without such vulnerability, *potentially indicating* that open and detailed questioning of [intrusive and] sensitive topics is not harmful and may even be beneficial." Nugent et al., *supra* note 18, at 446 (emphasis added) (discussing Widom & Czaia, *supra*, at 134). This is an unfounded inference and consequential conclusion (especially given the fact that Widom & Czaja explicitly stated that their research was limited and not generalizable to other kinds of research), not only about the benefit received by participants from being provided an opportunity to talk about trauma (one of the most important therapeutic tools for PTSD—but research is not therapy), but also in failing to address potential latent harms to patients from "detailed questioning of sensitive topics" without appropriate therapeutic guidance to work through the sensitive information they had shared. *Id.* (discussing Widom & Czaia, *supra*, at 136).

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Figure 1: Proposed Guidance

PARTICIPANTS PRESENTLY OR HISTORICALLY SUFFERING FROM MENTAL ILLNESS

If the study under review specifically targets or allows for enrollment of individuals who suffer from or have a history of suffering from mental illness:

DECISIONAL CAPACITY +

Even if an individual is determined by means of widely accepted assessment tools to possess decision-making capacity, if that individual is a person who suffers from or has a history of suffering from mental illness, extra steps must be taken to ensure voluntarism/autonomous consent.

ASCERTAINING VOLUNTARISM/AUTONOMOUS CONSENT

To ensure voluntarism/autonomous consent, the protocol must demonstrate how the investigator will ascertain:

1) Whether the potential participant's judgments, preferences, or personality are or might be altered by mental illness;
2) Whether the potential participant's judgments, preferences, or personality are or might be altered by psychotropic medications;
3) Whether the potential participant's decisions are or might be influenced by negative social, economic, or emotional consequences of stigma, isolation, societal discrimination and abuse, low self-confidence, or low self-worth; and
4) Whether the potential participant's decisions are or might be influenced by power differentials leading to unquestioning trust in the psychiatrist-researcher or distrust of self.

In instances where none of the above 4 factors are present, the investigator will be permitted to enroll the participant based solely on assessment of decision-making capacity.

WHERE VOLUNTARISM/AUTONOMOUS CONSENT ARE QUESTIONABLE

In anticipation of instances where any of the above 4 factors are present, the IRB must determine if the study investigator *specifically and adequately* demonstrates in the protocol how extra and appropriate protections, support, and education will be provided to individual potential participants suffering from or with a history of suffering from mental illness to ensure that enrollment is a voluntary, autonomous choice.

If no, the IRB should prohibit enrollment of these individuals because there are no measures in place to counteract and remedy questionable consent;

If yes, the IRB should potentially permit enrollment of these individuals after determining that the measures in place will counteract and remedy questionable consent
provided that
the protocol also describes with specificity the investigator's plans and mechanisms for providing ongoing protections, support, and education for these individual participants *and* for obtaining reconsent[196] throughout the life of the study.

To consistently and comprehensively implement this proposed guidance, IRBs and investigators would benefit from consensus on assessment of voluntarism/autonomous consent, and standardized tools such as template language for protocols and consents.

[196] Given the changes to one's mind in many mental illnesses, reconsent would provide an opportunity for participants to express a change of choice if they changed their mind about participation.

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To realize additional well-informed and meaningful policy changes, HHS should assemble and seek advice from a panel of lay experts—people who live with, or have a close connection to another who lives with, mental illness. HHS should ask what members of this population want researchers to consider. Involving those who have experienced or witnessed psychiatric crises would be especially useful, as these individuals have meaningful perspective on living through decompensation and coming out the other side, and the effects of various interventions and circumstances along the way. While mental health advocacy organizations could also be consulted, any ties to large pharmaceutical corporations should disqualify such groups from providing input, as the sponsorship and influence of these corporations may lead to bias and conflicts of interest.[197] No solution will be perfect: the goal should be to craft policy approaches that first listen to those who have personal experience with mental illnesses, and then use information gathered to better protect this community in biomedical research.[198]

B. People with Mental-Illness Experience are Integral to Research Review Process

People who have experienced a mental illness crisis and now manage their illness reasonably well truly know the vulnerability both of being in crisis and carrying the sometimes constant worry of relapse.[199] Recovery is a balancing act, and who would know better the competing forces and challenges of slogging through life with mental illness than those who live that experience each day?[200] The idea of involving affected populations in research related to their communities is not new. In fact, academic researchers in the United Kingdom are required, and private industry researchers strongly encouraged, to involve mentally ill people in research affecting their community.[201] Such approaches for involvement from the very early stages of research—even research idea

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[197] Martha Rosenberg, *Pharma Funding Advocacy Groups*, U. Southern Cal. Annenberg: Ctr. for Health Journalism (Oct. 15, 2014), https://www.centerforhealthjournalism.org/2014/10/15/discredited-patient-group-fights-mental-illness#:~:text=The%20patient%20front%20groups%20include,to%20the%20Wall%20Street% 20Journal [https://perma.cc/XM4A-HBQQ]. Large pharmaceuticals corporations have had their share of representation and influence already.

[198] Suggestions have been offered in the context of consent in clinical care and in the treatment of mentally ill patients, where the traditional MacArthur criteria for decision-making capacity have been perceived as insufficient. *See* Goldberg, *supra* note 64, at 11 ("The ability to govern along one's own self-narrative can, and therefore should, be clinically assessed and qualified. Although palpably absent from the current MacArthuer criteria, it is crucial to an assessment of self-governing capacity.").

[199] One participant in a recent study interviewing people who live with mental illness conveyed that "mental illness never completely disappears from one's life and can always potentially reemerge." Lajoie et al., *Enriching our Understanding*, *supra* note 24, at 448. Another participant in this same study offered that "[s]he has 'accepted herself as a vulnerable person' and knows that she needs to be vigilant and develop strategies to protect herself." *Id.* at 447.

[200] A current movement in the United States involves the use of Mental Health Peer Specialists in the treatment and recovery process of people with severe mental illness. *See* Matthew Chinman et al., *Establishing a Research Agenda for Understanding the Role and Impact of Mental Health Peer Specialists*, 68 Psychiatric Servs. 955, 955 (2017). These peer specialists are people who themselves live with mental illness. *Id.* The position of "peer specialist" has been professionalized through training and certification, and services are covered by Medicaid in over 30 states. *Id.* There is, however, a call for further research on the benefits of using peer specialists. *Id.*; *see also* Fortuna, *supra* note 15, at 580 ("Initial insights from this study can be used to guide researchers' efforts to incorporate certified peer specialists perspectives in developing programs to meet the needs of people with SMI.").

[201] *See* Sapfo Lignou et al., *Ethical Challenges in Research, Industry and People Partnerships in Mental Health* 1-2 (OSF Preprints, 2020) (quoting *Make a Strong Application*, Nat'l Inst. for Health Res., https://www.nihr.ac.uk/researchers/apply-for-funding/how-to-apply-for-project-funding/make-a-strong-application.htm [https://perma.cc/8NGM-JLGF]), https://osf.io/uwstp [https://perma.cc/2BK9-SAZU].

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generation—are admirable, but requiring such involvement in the United States would entail a major restructuring of how we conduct publicly funded research. While worthy of serious contemplation in the United States, extensive revamping of research regulations is beyond the scope of this Article and not a feasible option for promptly addressing the issues presented here.[202]

In the absence of HHS revising the rCR, clarifying definitions or providing guidance on enrollment of mentally ill people in research, or in addition to such actions, this Article proposes a modification to how IRBs are assembled in order to enhance representation of potentially vulnerable mentally ill participants. The proposal could be implemented as a policy measure not subject to public comment and the official rulemaking process. A template exists in the National Institutes of Health's ("NIH") restructuring of its former institute-specific IRB system into a centralized Intramural IRB.[203] In eliminating institute-specific protocol reviews, the NIH implemented a mechanism to ensure scientific expertise is represented at each IRB table: physicians and scientists from the various institutes may be called upon for more technical, disease-specific reviews.[204] These specialists are considered "subject matter experts," and whenever necessary, subject matter experts will be appointed to IRB panels.[205] A similar arrangement could be implemented in recruiting IRB community members.

NBAC's 1998 recommendations to include people suffering from mental disorders or their advocates as IRB members were in line with historical international initiatives aimed at improving "the quality of research review by carefully attending to the concerns of particular communities of individuals" that may be vulnerable.[206] NBAC's recommendations[207] reflected an awareness that family members of those who may not be available or able to serve on IRBs are in a unique position to share perspectives and represent certain otherwise voiceless segments of the population in research ethics determinations.[208] Likewise in 2008 to 2009, the Secretary's Advisory Committee on Human Research Protections ("SACHRP") approved similar recommendations by the

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[202] However, the Author advocates elsewhere that for genetics and genomics research relating to vulnerable or historically stigmatized populations (which would include people with mental illness) new governance approaches that include affected community members in decisions about research topics, design, recruitment, implementation, translation and dissemination are needed, especially when research results may lead to downstream harms to that community domestically and/or abroad. *See* Lisa E. Smilan, *Balancing Benefits and Harms of Sexual Orientation and Gender Identity Genomics Research: Legal and Life Implications*, 50 U. BALT. L. REV. (forthcoming Dec. 2020).

[203] Michael Gottesman & Richard Wyatt, *IRBs at NIH Revisited: Serving the Interests of Patients and Clinical Investigators*, 25 NIH CATALYST 2, 2 (2017).

[204] *Id.*

[205] *Id.*

[206] Françoise Baylis, *IRBs: Protecting the Well-Being of Subject-Participants with Mental Disorders That May Affect Decisionmaking Capacity*, 7 ACCOUNTABILITY IN RES. 183, 186 (1999). Note that in the United Kingdom, people with mental illness are involved in the planning process at the earliest stages for research affecting their community. *See* DEP'T OF HEALTH, A FRAMEWORK FOR MENTAL HEALTH RESEARCH 6 (2017) (U.K.) ("Recommendation 2: Patient and public involvement (PPI)"); *id.* pt. 4, at 19 ("[This initiative] includes involving members of the public in all stages of the research process, in activities such as priority setting, defining research outcomes, selecting research methodology, recruiting participants, interpretation of research findings and dissemination of results.").

[207] There is no need to "reinvent the wheel." The work of NBAC, leading to the 1998 *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity* report, is still quite relevant and could be built upon in any current efforts to better protect in the biomedical research arena those subjects who suffer from mental illness. NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 31.

[208] The Subcommittee on Inclusion of Individuals with Impaired Decision-making in Research (SIIIDR) was convened to develop recommendations regarding whether guidance and/or additional regulations were needed for research involving individuals with impaired decision-making capacity. SACHRP, *supra* note 48.

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Subcommittee on Inclusion of Individuals with Impaired Decision-making in Research ("SIIIDR"): "IRBs should give special consideration, as appropriate, to the involvement of the following types of individuals in the review process: i. Patients, former patients, patient advocates or family members or others who can represent the views and perspectives of the research participants."[209] Interestingly, in the Lawrence study, when asked whom they would consult regarding decisions about undergoing a DBS procedure, participants ranked close family members, romantic partners, and friends higher than psychiatrists, doctors, therapists, or experts in DBS.[210]

If former mental illness research participants are available and able, their voices at the IRB table surely would be invaluable. But, one need not have served as a research participant to have pertinent information on the unique concerns mentally ill research participants may have. A family member who has spent a dozen years securing medical treatment and medication for a patient suffering from bipolar disorder or schizophrenia will surely possess knowledge of participants' specific needs. Further, a person who lives with mental illness themselves and is in remission—though never a research participant—would bring highly pertinent perspective to the research review process. Official guidance and clear definitions would be of substantial value; however, institutions and their IRBs could move immediately to work on and implement positive changes. Simply changing *who* is at the IRB table interpreting regulations and guidance is a feasible way to more appropriately represent mentally ill people in research.[211]

As noted above, under its new IRB structure, the NIH matches physician and scientist subject matter experts to specific protocols in panel reviews.[212] Likewise, a similar "subject matter expert" or "subject matter area of interest" pairing of community members to protocols could be both appropriate and effective. Where a research institution maintains IRB community member pools, community members could be asked to specify areas of experience or interest, without being required to reveal their own protected health information or that of family members; these members could then be assigned to review protocols relating to their indicated experience and interest. Such targeted representation on clinical research protocol reviews would allow the institution to capitalize on the vast and varied knowledge bases of community members, increasing the likelihood that potentially vulnerable populations' unique needs are properly articulated, understood, and addressed. While taking some effort to set up, this modification would satisfy concerns about community representation without placing extra burdens on former research participants[213] who may not be well, able, or available to serve on IRBs.

VI. CONCLUSION

As clinical research with people who suffer from mental illness moves forward in new and exciting directions, eager anticipation of resulting benefits must be balanced by mindfulness of this community's history of stigmatization and abuse. Beyond common concerns about research with vulnerable populations, the prospects of using new technologies in research efforts aimed at curing psychiatric illness—e.g., gene editing—potentially will bring with them extreme risks and major ethics considerations; serious

[209] *Id.*

[210] Lawrence et al., *supra* note 1, at 214.

[211] *See* HARRIET A WASHINGTON, MEDICAL APARTHEID 401 (2006) (proposing "that each IRB be composed of equal numbers of scientists and of peers of the group who will be asked to participate as subjects.")

[212] *See* Gottesman & Wyatt, *supra* note 203.

[213] This is not to say that all people who live with mental illness would find participation burdensome.

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thought about special regulations for these new biotechnologies must begin in the near term.[214] Here and now, however, gaps in protections endure for mentally ill people in "ordinary" biomedical research, such as research using combinations of psychotropic medications that are not considered novel biotechnologies.

As recognized by many—including NBAC—during the past several decades, awareness and acknowledgment of the gaps in protections is required[215]: an earnest effort to resolve still unanswered questions about how adequately to protect mentally ill people in biomedical research is needed to finally close that gap. Unyielding adherence to traditional notions of decision-making capacity is a doorstop to closing the gaps in protections because other potential vulnerabilities to coercion or undue influence for mentally ill participants will remain unaddressed and ignored.

Standing alone, the rCR is not problematic; rather, it is the misguided application of the rule in the context of mental illness. Perhaps those in positions to interpret the rule, e.g., busy professionals at research institutions, are taking the most direct path to save time and simplify approaches to protect against vulnerabilities to coercion or undue influence. It is doubtful these approaches stem from lack of care about people who live with mental illness, and more likely that decisions are influenced by lack of time. Choices on implementation of protective policy that lean toward expediency, however, may leave unfulfilled the duty to protect people with mental illness in biomedical research.

Forty years after the Belmont Report, even with the 2018 revisions in the rCR, "we remain without sufficiently thorough policy guidelines for working with persons [who suffer from] mental illness."[216] Perhaps in the next round of rulemaking, if ever that happens, the rCR will be further revised to address these deficiencies. Some scholars have encouraged an alternative approach of more frequent modifications to the Common Rule, facilitated by mechanisms such as framework rulemaking and strategic consultation.[217] Rather immediately, new guidance and policies could interpret the regulations in ways allowing novel approaches to safeguard potentially vulnerable participants.[218]

In any event, it is important to recognize that most of the literature on the acceptability of research with mentally ill people is produced by researchers who conduct research on psychiatric interventions, some of which is sponsored by major

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[214] The Author's current work-in-progress focuses on this prospective concern. *See* Lisa Smilan, *Rethinking Regulation in the Context of New Biologic Drugs: Psychiatric Polygenic Risk Scores, Somatic Genome Editing & Legal Off-Label Uses* (forthcoming).

[215] NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 31, at 1-2.

[216] Williams, *supra* note 71, at 222.

[217] Benjamin E. Berkman et al., *A Proposed Process for Reliably Updating the Common Rule*, 17 AM. J. BIOETHICS 8, 12 (2017). For example, the rCR instructs "agencies that implement the Common Rule to collaborate on a process of redefining the definitions of 'identifiable private information' and 'identifiable biospecimen' at least every 4 years." *Id.* (quoting Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,149, 7,169 (Jan. 19, 2017) (to be codified at 45 C.F.R. pt. 46)).

[218] The National Institute of Mental Health (NIMH) has created the Human Subjects Protection Unit with Clinical Research Advocates (CRAs). NAT'L INST. OF MENTAL HEALTH, HUMAN SUBJECTS RESEARCH PROTECTIONS TOOLKIT 1.2 (2019). CRAs support individual subjects and provide education and advice to researchers. *Id.* NIMH has created a Toolkit, available for use and/or modification by outside organizations, based on "NIMH's experience conducting research with potentially vulnerable subjects [with the aim] to help research organizations assess, implement, and refine appropriate levels of human subjects protections during all phases of research." *Id.* Note, however, that the Toolkit is not to be construed as official interpretation of federal policy. While the Toolkit and CRAs are positive steps for built-in protections in the clinical research endeavor for subjects who suffer from mental illness, CRAs work with both subjects and researchers: for this reason (at least from a distance without intimate knowledge of the innerworkings of this office) CRAs may more closely resemble mediators than advocates and, thus, cannot substitute for federal regulations or binding guidance specifically designed to protect those who are vulnerable to coercion or undue influence in relation to their mental illness.

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pharmaceutical corporations.[219] Further, strong support regarding the acceptability of such research comes from community advocacy groups that largely are sponsored by big pharmaceutical corporations.[220] Without imputing ill intent to these parties, their perspectives may be biased toward the argument that mentally ill people are unfairly and improperly excluded from research. Limiting considerations to traditional decision-making capacity may be appealing to drug manufacturers and the researchers they sponsor, but this approach is simply not enough. The challenge of finding the right balance is difficult, but that should not dissuade an attempt to do so.

While confusion persists about the meaning of vulnerability to coercion or undue influence in clinical research with mentally ill people, creativity is needed in formulating new approaches to facilitate important research on mental illness while protecting potentially vulnerable participants. No solution can or will be perfect. The most straightforward remedy would be for HHS to further revise the rCR or provide clarity on the parameters of "vulnerability due to coercion or undue influence" and what this concept might include in real-life circumstances. Additionally, HHS should clarify its stance on "impaired decision-making capacity" and its relation to mentally ill participants. Also needed is binding guidance, like that suggested in Part V, on how to expand our thinking about mentally ill research participants' vulnerabilities to coercion or undue influence, beyond traditional consent-based decision-making capacity. HHS should speak to the practical application of these concepts so as to afford appropriate and consistent protections for mentally ill research subjects. In the absence of specific HHS leadership, or in addition to such guidance, changes in federal agency policies could require that any IRB reviewing protocols for research with this community must include affected people in remission or family members of severely mentally ill people.

Looking to community members who possess experience-based knowledge about mental illness and who, thus, may appropriately represent the interests of future participants would be a major step toward progress. These stakeholders should be invited to participate in the process of brainstorming, planning, and drafting binding guidance, beyond the traditional public comment for regulatory changes. Asking stakeholders—including community members in remission or family members of those struggling—to assist HHS in determining necessary changes, and bringing these same groups to the IRB table to review research, will enhance protections for potential research participants who are suffering from mental illness and unable themselves to pull up a chair.

[219] "Journals have devolved into information laundering operations for the pharmaceutical industry." Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, 2 PLOS MED. 364, 364 (2005) (quoting Richard Horton, *The Dawn of McScience*, N.Y. REV., Mar. 11, 2004 (reviewing SHELDON KRIMSKY, SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFITS CORRUPTED BIOMEDICAL RESEARCH? (2003))).

[220] *See* Rosenberg, *supra* note 197.

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