Washington Law Review

Volume 94 | Number 2

6-1-2019

Respecting the Right to Research: Proxy Consent and Subject Assent in Alzheimer's Disease Clinical Trials

Mikaela L.J. Louie

RESPECTING THE RIGHT TO RESEARCH: PROXY CONSENT AND SUBJECT ASSENT IN ALZHEIMER'S DISEASE CLINICAL TRIALS

Mikaela L. J. Louie*

Abstract: Alzheimer's Disease is the sixth-leading cause of death in the United States and the only disease in the top ten causes of death with no prevention, treatment, or cure. To find any meaningful treatment or cure, researchers must conduct clinical trials on subjects with Alzheimer's Disease. Subjects with Alzheimer's Disease, however, generally lack legal capacity to consent to research due to diminished cognition. While informed consent standards for individuals who lack capacity are well settled in the medical treatment context, such standards are much less clear in the research context. A patchwork of legal and regulatory guidance addresses this issue, but no uniform framework exists.

In January 2017, the federal government responded to the problem of unclear proxy consent standards by updating the Common Rule, which regulates human subjects research. Attempting to clarify prior vagueness, the regulation extended existing laws and policies on proxy consent in clinical treatment to the research context. While this was a welcome change, state laws and institutional policies remain inconsistent. Therefore, states should affirmatively enact legislation to ensure inclusion for all participants in medical research. Practically, this may be as simple as amending existing health care surrogate decision-making statutes—allowing proxy consent and substituted judgment in the research context explicitly. Additionally, federal regulators, Institutional Review Boards, and researchers should consider establishing an assent and dissent standard for research subjects who lack capacity, specifically in Alzheimer's Disease clinical trials.

So how could I be mad? She was setting the example, as she had done her whole life, her whole career, without pessimism or regret, or fanfare, just ready to go on, even though her words and steps might mutate, unpredictably, ever aware of the possible endpoints, with each of us now grappling this present moment, trying to recognize its identity.
—Ron Louie, M.D., Clinical Professor,
University of Washington[1]

---

* J.D. Candidate, University of Washington School of Law, Class of 2019. This Comment is dedicated to IRJ and RRL. Thank you to Terry Price and the *Washington Law Review* editorial staff for their support and feedback. I serve as a volunteer member of the Board of Directors for Alzheimer's Association, Washington State and Northern Idaho Chapter. All opinions and omissions are my own.

1. Ron Louie, *Matter of Fact*, 90 NEUROLOGY 139 (2018) (medical poem recounting early onset AD diagnosis experience).

INTRODUCTION

In 2011, Congress passed the National Alzheimer's Project Act (NAPA) to address a growing public health and economic crisis.[2] An estimated 5.5 million individuals in the United States are currently living with Alzheimer's Disease (AD).[3] AD is the only disease in the nation's top ten causes of death that cannot be prevented, treated, or cured.[4] The disease kills more people than breast cancer and prostate cancer combined.[5] Beyond the physical and emotional toll, AD is tremendously expensive.[6] In 2017 alone, AD cost the United States $259 billion.[7] Considering these challenges, NAPA set out lofty goals, aspiring to treat and prevent AD by 2025.[8] With the NAPA target date rapidly approaching and the list of research failures growing daily,[9] policymakers, government agencies, and researchers must implement changes in AD research.

Physicians are trained to treat illness and, with the advancement of modern medicine, are increasingly expected to cure disease.[10] Individuals living with AD, however, cannot rely on the expectation of treatment or cure.[11] Other major diseases like cancer and HIV-AIDS held the same dire status of incurable disease years ago but have since

---

2. National Alzheimer's Project Act, Pub. L. No. 111-375, 124 Stat. 4100 (2011) (codified at 42 U.S.C. § 11225 (2018)). The statute designates the Secretary of Health and Human Services as the implementer of an integrated national plan and coordinator of Alzheimer's research and services across all Federal agencies. 42 U.S.C. § 11225; *see also id.* § 11201 (providing statistics illustrating Congress's findings).

3. Alzheimer's Ass'n, *2017 Alzheimer's Disease Facts and Figures*, 13 ALZHEIMER'S & DEMENTIA 325, 334 (2017) (discussing how the estimated number of people with Alzheimer's dementia comes from the latest 2010 U.S. Census data and the Chicago Health and Aging Project (CHAP), though noting that "Alzheimer's dementia is underdiagnosed and underreported").

4. *Id.* at 340.

5. *Id.* at 325.

6. *See id.* at 325, 340; David H. Freedman, *The Missing Alzheimer's Pill*, POLITICO (Dec. 13, 2017, 5:19 AM), https://www.politico.com/agenda/story/2017/12/13/drug-industry-new-developments-000598 [https://perma.cc/65MY-MHY5].

7. Alzheimer's Ass'n, *supra* note 3, at 350 (Medicare: $131 billion; Medicaid: $44 billion; out of pocket: $56 billion; and other: $28 billion).

8. National Alzheimer's Project Act, Pub. L. No. 111-375, § 2(e), 124 Stat. 4100, 4101–03 (2011) (codified at 42 U.S.C. § 11225 (2018)).

9. Damian Garde, *Pharma's Latest Alzheimer's Failure Comes with a Particular Sting*, STAT (Feb. 13, 2018), https://www.statnews.com/2018/02/13/pharmas-alzheimers-failure-merck/ [https://perma.cc/9KFQ-HQ6E].

10. *See* David Epstein & Propublica, *When Evidence Says No, but Doctors Say Yes*, ATLANTIC (Feb. 22, 2017), https://www.theatlantic.com/health/archive/2017/02/when-evidence-says-no-but-doctors-say-yes/517368/ [https://perma.cc/Q4ZJ-79HL].

11. Alzheimer's Ass'n, *supra* note 3, at 340.

enjoyed remarkable progress.[12] Yet, AD has seen little progress despite decades of research attempts,[13] rising public awareness, increased funds,[14] and other regulatory changes.[15]

AD is an "irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks."[16] AD is a specific disease that falls under the broader category of dementia; it is the most common cause of dementia among older adults.[17] Dementia is the "loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities to such an extent that it interferes with a person's daily life and activities."[18] Dementia "ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of living."[19]

The AD cognitive decline ultimately renders an individual legally incapacitated. In the eyes of the law, an individual with later stage AD lacks the capacity to make decisions or provide informed consent.[20]

---

12. Steven G. Deeks et al., *The End of AIDS: HIV Infection As a Chronic Disease*, 382 LANCET 1525–33 (2013) (discussing "[t]he success of antiretrovial therapy," and how "[t]he idea of HIV as a chronic disease has emerged as a result of advances in treatment in the past three decades"); Rebecca L. Siegel, Kimberly D. Miller & Ahmedin Jemal, *Cancer Statistics, 2018*, 68 CA: CANCER J. FOR CLINICIANS 7 (2018) ("The combined cancer death rate dropped continuously from 1991 to 2015 by a total of 26%, translating to approximately 2,378,600 fewer cancer deaths than would have been expected if death rates had remained at their peak.").

13. Maria Burke, *Why Alzheimer's Drugs Keep Failing*, SCIENTIFIC AM. (July 14, 2014) (originally published in CHEMISTRY WORLD (July 3, 2014)), https://www.scientificamerican.com/article/why-alzheimer-s-drugs-keep-failing/ [https://perma.cc/8H7Z-ZDAX]; John Carroll, *Merck's Leading Ph111 BACE Drug Implodes in Latest Alzheimer's Disaster*, ENDPOINTS NEWS (Feb. 15, 2017, 11:13 AM), https://endpts.com/mercks-leading-phiii-bace-drug-implodes-in-latest-alzheimers-disaster/ [https://perma.cc/ML9P-M36C]; Freedman, *supra* note 6; Melissa Healy, *One of the Most Promising Drugs for Alzheimer's Disease Fails in Clinical Trials*, L.A. TIMES (Jan. 9, 2018, 3:55 PM), https://www.latimes.com/science/sciencenow/la-sci-sn-alzheimers-drug-fail-20180109-story.html [https://perma.cc/RX5D-RWML] ("Idalopirdine, an experimental drug that seemed one of the most promising candidates to treat Alzheimer's disease, failed several phase 3 clinical trials.").

14. *See* Consolidated Appropriations Act, 2017, Pub. L. 115-31, 131 Stat. 135 (increasing National Institute on Aging AD research funding by $400 million).

15. *See* Early Alzheimer's Disease: Developing Drugs and Treatment: Draft Guidance for Industry, 83 Fed. Reg. 7060 (Feb. 16, 2018) (proposing accelerated approval by considering biomarker data and cognitive evaluations).

16. *What Is Alzheimer's Disease?*, NAT'L. INST. ON AGING, (Dec. 31, 2017), https://www.nia.nih.gov/health/what-alzheimers-disease [https://perma.cc/D5WD-Z33D].

17. *Id.*

18. *Id.*

19. *Id.*

20. *See In re* Denison's Estate, 23 Wash. 2d 699, 706, 716–19, 162 P.2d 245, 248, 253–54 (1945).

States have responded to this phenomenon by enacting legislation establishing elaborate schemes of surrogate decision making.[21] Twenty-six states have enacted the Uniform Power of Attorney Act[22] to create default rules in case of future incapacity.[23] Fewer than a dozen states, however, specifically address proxy consent in the research context.[24] At the federal level, regulations on human subjects research, known as the "Common Rule," remained vague on proxy consent for years.[25] Despite a Common Rule update in 2017 attempting to clarify prior vagueness, the change does little beyond leaving it to the states and "institutional policy" (e.g., Institutional Review Boards (IRBs)).[26] Ultimately, confusion will persist because state laws vary widely on surrogate decision-making standards,[27] and IRBs are inconsistent in their proxy consent practices.[28]

This Comment examines the current legal and regulatory frameworks addressing consent for individuals who lack capacity in the biomedical research context and argues for a uniform approach. Part I examines the doctrine of informed consent, legal standards for surrogate decision making, and the development of these standards in the medical treatment context. Part II explores how the informed consent doctrine manifests in the biomedical research context, specifically in inconsistent regulatory frameworks and state statutes. Part II also outlines possible

---

21. *See* ABA COMM'N ON LAW & AGING, DEFAULT SURROGATE CONSENT STATUTES (2018), https://www.americanbar.org/content/dam/aba/administrative/law_aging/2014_default_surrogate_consent_statutes.authcheckdam.pdf [https://perma.cc/3CQN-CUA5].

22. UNIF. POWER OF ATT'Y ACT (NAT'L CONFERENCE OF COMM'RS ON UNIF. STATE LAWS 2006), https://comm.ncsl.org/productfiles/83335813/UPOAA_2011_FinalAct_2014sep9.pdf [https://perma.cc/F5MN-MXY5].

23. *Power of Attorney Act*, UNIFORM L. COMMISSION, https://my.uniformlaws.org/committees/community-home?CommunityKey=b1975254-8370-4a7c-947f-e5af0d6cb07c (last visited Apr. 30, 2019).

24. *See* CAL. HEALTH & SAFETY CODE § 24178 (West 2019); 410 ILL. COMP. STAT. 50/3.1(b) (2019); KAN. STAT. ANN. § 65-4974 (2019); MO. REV. STAT. §§ 431.064, 630.115 (2019); N.J. STAT. ANN. § 26:14-5 (West 2019); OKLA. STAT. ANN. tit. 63, § 3102A (West 2019).

25. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,149, 7,170–71 (Jan. 19, 2017) (codified in scattered parts of 6, 7, 10, 14, 15, 20, 22, 24, 29, 32, 34, 38, 40, 45, 49 C.F.R.).

26. *Id.* at 7,170–71, 7,260.

27. ABA COMM'N ON LAW & AGING, *supra* note 21.

28. Michelle Ng Gong et al., *Surrogate Consent for Research Involving Adults with Impaired Decision Making: Survey of Institutional Review Board Practices*, 38 CRITICAL CARE MED. 2146, 2146 (2010) (discussing how 6% of IRBs "do not accept surrogate consent for research from any persons, and 22% of [IRBs] accept only an authorized proxy, spouse, or parent as surrogates, excluding adult children and other family. [IRBs] vary in their limits on research risks in studies involving incapacitated adults: 15% disallow any research regardless of risk in studies without direct benefit, whereas 39% allow only minimal risk.").

modifications to informed consent for subjects with AD, including assent and dissent standards as used for minors participating in clinical research. Part III describes the state of AD research and how researchers seek consent from subjects with AD. Finally, Part IV argues for the adoption of proxy consent in medical research statutes and other informed consent modifications to ensure effective, efficient, and respectful participation in later-stage AD clinical trials.

I. INFORMED CONSENT AND SURROGATE DECISION MAKING IN MEDICAL TREATMENT

While the concept of informed consent is rooted in medical ethics, it is inherently a legal construct.[29] This Part first examines the development of informed consent in common law. It then explores two primary legal standards for surrogate decision making: substituted judgment and best interests. Finally, it discusses how *Cruzan v. Director, Missouri Department of Health*,[30] an instrumental U.S. Supreme Court case, led to the utilization of advance directives and Durable Power of Attorney statutes.[31]

A. The Evolution of Informed Consent in Common Law

The legal doctrine of informed consent is grounded in principles of patient autonomy and individual rights.[32] Traditionally, patients followed "doctor's orders" without question.[33] A change in these "traditional patterns of communication between doctors and patients came not from medicine but from law."[34] In 1914, then-judge Benjamin N. Cardozo articulated the informed consent proposition in the treatment context:

> Every human being of adult years and *sound mind* has a right to determine what shall be done with his own body; and a surgeon

29. Jay Katz, *Informed Consent — Must It Remain a Fairy Tale?*, 10 J. CONTEMP. HEALTH L. & POL'Y 69, 77 (1994).

30. 497 U.S. 261 (1990).

31. *See In re* Guardianship of Schiavo, 780 So. 2d 176, 178 (Fla. 2001) (citing to a Florida statute stating "[w]hen a living will or other advance directive does not exist, it stands to reason that the surrogate decision-maker will be a person who is close to the patient and thereby likely to inherit from the patient"); Charity Scott, *Why Law Pervades Medicine: An Essay on Ethics in Health Care*, 14 NOTRE DAME J.L. ETHICS & PUB. POL'Y 245, 268–69 (2000); Tamar Lewin, *Nancy Cruzan Dies, Outlived by a Debate Over the Right to Die*, N.Y. TIMES, Dec. 27, 1990, at A15.

32. *See* Cathy J. Jones, *Autonomy and Informed Consent in Medical Decisionmaking: Toward a New Self-Fulfilling Prophecy*, 47 WASH. & LEE L. REV. 379, 385 (1990).

33. Katz, *supra* note 29, at 74.

34. *Id.* at 77.

> who performs an operation without his patient's consent commits an assault, for which he is liable in damages. This is true, except in cases of emergency where the patient is unconscious, and where it is necessary to operate before consent can be obtained.[35]

Informed consent jurisprudence evolved from this early concept. In 1957, a California court coined the term "informed consent," holding that "a physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by [the] patient to [the] proposed treatment."[36]

In *Canterbury v. Spence*,[37] a young man sought medical treatment for back pain.[38] The patient's physician determined that a simple procedure was necessary to treat the pain.[39] During the operation, the physician realized that the patient had a more serious spinal issue and performed a more invasive surgery.[40] During recovery, the patient—not knowing that the doctor had performed a more invasive surgery—fell out of his hospital bed and became partially paralyzed.[41] In this seminal case, the D.C. Circuit held that informed consent is based on the patient's perspective, not the medical community's standard of reasonableness.[42] In other words, the scope of informed consent must be "measured by the patient's need," which critically encompasses "information material to the decision" of accepting any given treatment.[43] The court noted that "[t]he average patient has little or no understanding of the medical arts, and ordinarily has only his physician to whom he can look for enlightenment with which to reach an intelligent decision."[44]

B. Informed Consent for Individuals Who Lack Capacity

Cardozo's principle of informed consent applied to adults of "sound mind."[45] Due to the significance of autonomy, "it is well-settled that the

35. Schloendorff v. Soc'y of N.Y. Hosp., 105 N.E. 92, 93 (N.Y. 1914) (emphasis added) (citation omitted).

36. Salgo v. Leland Stanford Junior Univ. Bd. of Trs., 317 P.2d 170, 181 (Cal. Ct. App. 1957).

37. 464 F.2d 772 (D.C. Cir. 1972).

38. *See id.* at 776.

39. *Id.*

40. *Id.* at 777.

41. *Id.* at 777–78.

42. *Id.* at 783–86.

43. *Id.* at 786.

44. *Id.* at 780.

45. Schloendorff v. Soc'y of N.Y. Hosp., 105 N.E. 92, 93 (N.Y. 1914).

law presumes adult persons are . . . capable, rather than incapable, to direct their personal affairs until satisfactory evidence to the contrary is presented."[46] A variety of factors determine a person's ability to be autonomous.[47] When an individual no longer possesses those abilities, they are judged legally incapacitated.[48] As one court describes:

> Incapacity is the legal status that occurs when a person's autonomy becomes either partially or totally impaired. A person lacks the ability to be autonomous—to exercise free will—when he or she lacks the ability to absorb information, to understand its implications, to correctly perceive the environment, or to understand the relationship between his or her desires or actions. A person is likewise incapacitated when he or she cannot control his or her actions or behavior.[49]

Thus, legal incapacity may occur as a result of any number of medical conditions. In addition to AD, courts may consider individuals with other conditions (e.g., severe mental illness, schizophrenia, traumatic brain injury, brain dead, terminally ill) legally incapacitated.[50]

Informed consent for incapacitated patients caught the nation's attention with a series of cases involving women in persistent vegetative states (PVS).[51] In one landmark case, Nancy Cruzan laid in a PVS after a terrible car accident.[52] When Cruzan's parents attempted to terminate life-support, state hospital officials refused based on state policy.[53] The Supreme Court of Missouri ruled in favor of the state policy over the

---

46. *In re* Conservatorship of Groves, 109 S.W.3d 317, 329–30 (Tenn. Ct. App. 2003).

47. *Id.* at 328–30.

48. *Id.*

49. *Id.* at 328–29.

50. *See* Sameer S. Apte, *Blood Substitutes-The Polyheme Trials*, 11 MCGILL J. MED. 59, 61 (2008) (treating unconscious patients as legally incapacitated in emergent situations, when "obtaining informed consent from a legally authorized representative [is] infeasible given the time frame in which the subject must be treated"); Debra L. Dippel, *Someone to Watch Over Me: Medical Decision-Making for Hopelessly Ill Incompetent Adult Patients*, 24 AKRON L. REV. 639, 640 (1991).

51. *See, e.g.*, Cruzan v. Dir., Mo. Dep't of Health, 497 U.S. 261, 262 n.1, 266 (1990) (discussing how Cruzan, who sustained serious injuries from an automobile accident, "now lies in a Missouri state hospital in what is commonly referred to as a persistent vegetative state"); *In re* Guardianship of Schiavo, 780 So. 2d 176, 177 (Fla. 2001) ("Theresa [Schiavo], age 27, suffered a cardiac arrest as a result of a potassium imbalance. . . . The evidence is overwhelming that Theresa is in a permanent or persistent vegetative state."); *In re* Quinlan, 355 A.2d 647, 651 (N.J. 1976) ("At the age of 22, [Quinlan] lies in a debilitated and allegedly moribund state . . . .").

52. *Cruzan*, 497 U.S. at 266–68.

53. *Id.* at 267–68.

family's right to refuse treatment.[54] Ultimately, the U.S. Supreme Court found that while "the common-law doctrine of informed consent is viewed as generally encompassing the right of a competent individual to refuse medical treatment,"[55] this right did not extend to incompetent persons absent "clear and convincing" evidence that the patient—in this case, Cruzan—personally desired to withdraw treatment.[56] On remand, the family ultimately proffered enough evidence of Cruzan's preferences to withdraw life-sustaining treatment.[57]

Nevertheless, state and federal law recognizes an incompetent individual's right to autonomy and self-determination.[58] If a patient is deemed legally incapacitated to consent, there are several options for third party decision makers.

1. Surrogate Decision-Making Standards

All fifty states have enacted surrogate health care decision-making statutes.[59] Each state law, however, varies with respect to: (1) limitations on surrogate decision making; (2) the appropriate legal standard; and (3) provisions addressing patients with no available qualified surrogate.[60] Prior to state statutory enactments, courts approved surrogate consent.[61] Whether executed as a Durable Power of Attorney (DPOA) for health care or by state statute, regulation and law generally refers to a surrogate decision maker as a "legally authorized representative" (LAR) in the research context.[62]

Generally, surrogate decision-making statutes authorize a list of surrogates in lieu of a patient-designated person.[63] Many states list default surrogates in order by familial relationship.[64] For example,

54. *Id.* at 268.

55. *Id.* at 277.

56. *Id.* at 284.

57. Lewin, *supra* note 31, at A1.

58. WASH. STATE HOSP. ASS'N, END OF LIFE CARE MANUAL § 5 (2015), http://www.wsha.org/wp-content/uploads/End-of-Life-Care-Manual.pdf [https://perma.cc/68ZX-9HN2].

59. ABA COMM'N ON LAW & AGING, *supra* note 21; Dippel, *supra* note 50.

60. ABA COMM'N ON LAW & AGING, *supra* note 21.

61. Diane E. Hoffmann, Jack Schwartz & Evan G. DeRenzo, *Regulating Research with Decisionally Impaired Individuals: Are We Making Progress?*, 3 DEPAUL J. HEALTH CARE L. 547, 581 (2000).

62. *See* 45 C.F.R. § 46.102(c) (2018).

63. *See* IDAHO CODE ANN. § 39–4504 (West 2019); OR. REV. STAT. ANN. §§ 127.505(13), 127.535(4), 127.635 (West 2019); WASH. REV. CODE § 7.70.065 (2019).

64. *See* OKLA. STAT. ANN. tit. 63, § 3102A(1)-(5) (West 2019); OR. REV. STAT. ANN. § 127.635(2)(a)–(g); WASH. REV. CODE § 7.70.065(1)(a)(iii)–(vi).

Washington State authorizes default surrogates as (1) spouse or registered domestic partner; (2) adult children; (3) parents; and (4) adult siblings.[65] California, however, does not contemplate a default system; it requires patients to orally designate a surrogate.[66]

In both statutes and court decisions, "the surrogate [is] expected to decide consistent with the patient's preferences and values (if known), or if not known, then consistent with what would be in the patient's best interest."[67] Generally, there are two primary standards for surrogate decision-making: "substituted judgment" and "best interest."[68] The medical community continues to debate which legal decision-making standard is best for patients.[69] Furthermore, many states have no articulated decision-making standard for guardians of incapacitated adults.[70]

a. The Substituted Judgment Standard

In a few states that have articulated decision-making standards, surrogates must make decisions following the substituted judgment standard.[71] Under substituted judgment, surrogates make decisions based on the patient's wishes with as much accuracy as possible.[72] If the patient did not expressly convey such wishes (e.g., in an advanced directive), the surrogate must make an inference based on the patient's statements and conduct prior to incapacity.[73]

Without a designated surrogate, physicians may also turn to courts for "substituted judgment."[74] One Washington state court held that a trial

65. WASH. REV. CODE § 7.70.065(1)(a)(iii)–(vi).

66. CAL. PROB. CODE § 4711 (West 2019).

67. Hoffmann et al., *supra* note 61, at 581.

68. *See* Lawrence A. Frolik & Linda S. Whitton, *The UPC Substituted Judgment/Best Interest Standard for Guardian Decisions: A Proposal for Reform*, 45 U. MICH. J.L. REFORM 739, 742 (2012).

69. *Compare* Alexia M. Torke, G. Caleb Alexander & John Lantos, *Substituted Judgment: The Limitations of Autonomy in Surrogate Decision Making*, 23 J. GEN. INTERNAL MED. 1514, 1515–16 (2008) (advocating for best interest standard or an approach that focuses on dignity instead of autonomy), *with* Norman L. Cantor, *Discarding Substituted Judgment and Best Interests: Toward a Constructive Preference Standard for Dying, Previously Competent Patients Without Advance Instructions*, 48 RUTGERS L. REV. 1193, 1201–41 (1996) (rejecting both substituted judgment and best interest standards).

70. Frolik & Whitton, *supra* note 68, at 742.

71. *See id.* at 743 ("[E]ighteen jurisdictions include some type of substituted judgment language, fourteen of which also refer to best interest.").

72. *See id.* at 740; Torke et al., *supra* note 69, at 1514.

73. Shana Wynn, *Decisions by Surrogates: An Overview of Surrogate Consent Laws in the United States*, 36 BIFOCAL 10, 12 (2014).

74. *See In re* Schuoler, 106 Wash. 2d 500, 723 P.2d 1103 (1986).

court may order therapy for a nonconsenting patient only after considering and setting forth findings on: (1) the nature of the patient's desires; (2) whether the state has a significant interest in treatment; and (3) whether the therapy is necessary and effective to satisfy the state interest implicated.[75]

Moreover, "[t]he court should consider previous and current statements of the patient, religious and moral values of the patient regarding medical treatment and electroconvulsive therapy, and views of individuals that might influence the patient's decision."[76] If "the patient appears unable to understand fully the nature of the [treatment]—as severely mentally ill patients often are—the court should make a 'substituted judgment' for the patient that is analogous to the medical treatment decision made for an incompetent person."[77] Finally, the court should enter a finding on the nature of the patient's desires.[78] In other words, "[t]he goal is not to do what most people would do, or what the court believes is the wise thing to do, but rather what this particular individual would do if [they] were competent and understood all the circumstances, including [their] present and future competency."[79]

While surrogate decision makers and substituted judgment may reflect a paternalistic approach, there is a growing movement toward recognizing the autonomy of the decisionally impaired.[80] Not only are advocacy groups—including the disability rights movement and the Alzheimer's Association—active in the debate, but individuals who have mental illness and dementia have joined the conversation as well,[81] perhaps exhibiting the autonomy that they seek.

Arguments against substituted judgment focus on individuals' changing preferences over time.[82] A series of studies have shown that individuals change their wishes with regard to life-sustaining treatment throughout their lives.[83] Patients who complete advance directives,

---

75. *Id.* at 511, 723 P.2d at 1110.

76. *Id.* at 507, 723 P.2d at 1108.

77. *Id.* (citing *In re* Ingram, 102 Wash. 2d 827, 838–42, 689 P.2d 1363, 1369–71 (1984)).

78. *Id.*

79. *In re Ingram*, 102 Wash. 2d at 839, 689 P.2d at 1369.

80. Hoffmann et al., *supra* note 61, at 573; *see* Arlene Mayerson, *1970's and Onward—The Civil Rights Perspective*, *in* THE LEGAL RIGHTS OF CITIZENS WITH MENTAL RETARDATION 105 (Lawrence A. Kane, Jr. et al. eds., 1988).

81. Hoffmann et al., *supra* note 61, at 573–75.

82. Torke et al., *supra* note 69, at 1514.

83. *Id.*

however, are less likely to change their wishes.[84] Therefore, those individuals who have not expressed their wishes are the ones for whom substituted judgment is least likely to be accurate.[85]

b. The Best Interest Standard

When the patient's wishes are not or cannot be known, many states follow the "best interest" standard.[86] According to the best interest standard, the surrogate must make decisions that protect the patient's current and future interests.[87] The standard is inherently protectionist and paternalistic.[88] Courts have defined "best interests" in terms of what a "reasonable person" would decide in the same situation.[89]

Courts often apply the best interest standard to minors.[90] For example, if parents refuse "to authorize needed life-saving blood transfusions, doctors have a moral and legal duty to help the child and notify the courts."[91] Once the state proves, "often by clear and convincing evidence, that the child has suffered or is in danger of suffering serious harm," then judges may "choose the best available option for the child."[92]

The Washington State Supreme Court, however, applied this standard to an adult who never had the ability to form genuine preferences.[93] In *In re Hamlin*,[94] the court upheld the best interest standard for a terminally ill adult with severe mental impairment since birth.[95] In finding that the

84. *Id.*

85. *Id.*

86. *See, e.g.*, WASH. REV. CODE § 7.70.065(1)(c) (2019) ("[T]he [surrogate] must first determine in good faith that that patient, if competent, would consent to the proposed health care. If such a determination cannot be made, the decision to consent to the proposed health care may be made only after determining that the proposed health care is in the *patient's best interests*." (emphasis added)).

87. Dippel, *supra* note 50, at 668.

88. Nancy K. Rhoden, *Litigating Life and Death*, 102 HARV. L. REV. 375, 398–401 (1988).

89. Loretta M. Kopelman, *The Best Interest Standard for Incompetent or Incapacitated Persons of All Ages*, 35 J.L. MED. & ETHICS 187, 188 (2007).

90. *Id.*

91. *Id.*

92. *Id.*

93. *In re* Hamlin, 102 Wash. 2d 810, 819–20, 689 P.2d 1372, 1378 (1984); *see also id.* at 821, 689 P.2d at 1379 (recognizing that "[t]he problem before us involves social, moral and ethical considerations as well complex legal and medical issues for which the legislative process is best suited to address in a comprehensive manner").

94. *In re* Hamlin, 102 Wash. 2d 810, 819–20, 689 P.2d 1372, 1378 (1984).

95. *Id.*

individual never had the ability to form genuine preferences or express his wishes about the termination of life support, the court found that the best interest standard applied.[96]

Although surrogates should have a "*prima facie* duty" to "maximize the person's overall or long term benefits and minimize burdens"[97] under the best interest standard, it remains unclear whose determination controls—clinicians, surrogates, or courts.[98] In 2005, the President's Council on Bioethics[99] described surrogate decision-making duties under the best interest standard: "Ultimately, caregivers must compare the burdens, consequences, and potential complications of the *treatment itself* against the burdens, consequences, and potential complications of *non-treatment*; and they must compare the likely realities of *life after treatment* against the likely realities of *life without treatment*."[100]

Some scholars continue to advocate for the best interest standard for incompetent adults.[101] Recognizing the standard's inherent paternalism, refined approaches include basing "best interest" on community norms.[102] Most of this commentary, however, is focused on medical treatment or end of life decision making, not biomedical research.[103]

c. Hybrid Standard Model

At least fourteen state surrogate decision-making statutes mention both the best interest and the substituted judgment standards.[104] Three states that use both standards, however, do not indicate what relative weight surrogates are to give either standard.[105] In evaluating these

---

96. *Id.*

97. Kopelman, *supra* note 89, at 188 (arguing for the best interest standard).

98. *See id.*

99. Exec. Order No. 13,237, 66 Fed. Reg. 59,851 (Nov. 28, 2001) (establishing Council to advise the administration on bioethics consisting of no more than eighteen members appointed for two-year terms), *superseded by* Exec. Order No. 13,521, 74 Fed. Reg. 62,671 (Nov. 24, 2009) (establishing the Presidential Commission for the Study of Bioethical Issues).

100. PRESIDENT'S COUNCIL ON BIOETHICS, TAKING CARE: ETHICAL CAREGIVING IN OUR AGING SOCIETY 176 (2005).

101. *See* Torke et al., *supra* note 69, at 1515.

102. *Id.* (citing Rebecca Dresser, *Precommitment: A Misguided Strategy for Securing Death with Dignity*, 81 TEX. L. REV. 1823 (2003)).

103. *See id.*

104. Frolik & Whitton, *supra* note 68, at 743; Nina A. Kohn & Jeremy A. Blumenthal, *Designating Health Care Decisionmakers for Patients Without Advance Directives: A Psychological Critique*, 42 GA. L. REV. 979, 986 (2008); *see also* WASH. REV. CODE § 7.70.065(1)(c) (2019).

105. Frolik & Whitton, *supra* note 68, at 746.

statutes, scholars have recognized that all lacked adequate guidance for decision-making.[106] "Ironically, while dual mandate-type statutes . . . may deter unreasonable decisions, they also deprive incapacitated persons of the right to substituted judgments that produce reasonable outcomes."[107]

To establish a more workable standard, scholars Lawrence Frolik and Linda Whitton offer a model that breaks down the standards into "Expanded" and "Strict" categories and establishes a sliding scale.[108] With "Expanded Best Interest," "guardians may base their decisions on the benefits and burdens for the incapacitated person, as discerned from available information, including the views of professionals and others with sufficient interest in the incapacitated person's welfare."[109] Decisions may also include consideration of consequences for others that a reasonable person in the incapacitated person's circumstances would consider.[110] If following "Strict Best Interest," however, guardians should base their decisions solely on the benefits for, and burdens on, the incapacitated person as discerned from available information.[111]

2. Advance directives and Durable Powers of Attorney

Surrogate decision-makers may also rely on an incapacitated individual's advanced directive or durable power of attorney assignment.[112] *Cruzan* established a high evidentiary standard for patients' preferences prior to incompetence.[113] This decision partially led to the creation of advance directives as a tool for patients to execute their wishes before any future incompetence.[114] An advanced directive is a written contract that establishes an individual's medical wishes should they become incompetent or incapacitated.[115] Individuals may draft and sign an advanced directive while still competent, and it is enforceable if that person loses the ability to consent.[116] For example, the individual

106. *Id.* at 747.
107. *Id.* at 750.
108. *Id.* at 751–52.
109. *Id.* at 751.
110. *Id.*
111. *Id.* at 752.
112. *See* WASH. REV. CODE §§ 7.70.065(1)(a)(ii), 11.125.030 (2019).
113. *See* Cruzan v. Dir., Mo. Dep't of Health, 497 U.S. 261, 284 (1990).
114. *See* Scott, *supra* note 31, at 268–69.
115. *See id.* at 269; Dippel, *supra* note 50, at 664–66.
116. Dippel, *supra* note 50, at 665–66.

may express their wish to refuse or withhold life-sustaining treatment at a certain point.[117] Healthcare advance directives have become a standard part of estate planning, yet most forms do not include medical research wishes.[118]

The American Bar Association (ABA) Commission on Law and Aging offers a variety of advanced directive and surrogate decision-making resources.[119] The Commission's resources include guidance on choosing a health care proxy, a proxy quiz, and power of attorney forms.[120] None of these forms, however, mention or include any information on participating in research or clinical trials.[121]

Following the *Cruzan* decision, the ABA Commission on Law and Aging partnered with Aging with Dignity to develop an advance directives model to meet legal evidentiary requirements.[122] This work resulted in the popular "Five Wishes" model accepted in forty-two states.[123] Five Wishes includes two legal documents and other matters of comfort care and final wishes.[124] Wish 1 assigns a health care surrogate.[125] Wish 2 addresses what kind of end-of-life medical treatment a patient desires.[126] Nevertheless, none of the five wishes include research participation.[127]

To resolve the challenges of surrogate decision-making, individuals may elect to execute Durable Powers of Attorney (DPOA) for Health

---

117. *Id.* at 642.

118. *Id.*; *see Sample Health Care Directive (or Living Will)*, WASH. STATE HOSP. ASS'N, http://www.wsha.org/wp-content/uploads/End-of-Life_LivingWill.pdf [https://perma.cc/9RNR-NENB]; *Sample Durable Power of Attorney for Health Care*, WASH. STATE HOSP. ASS'N, http://www.wsha.org/wp-content/uploads/End-of-Life_Durable_Power_Attorney.pdf [https://perma.cc/C42A-KZ8A].

119. ABA COMM'N ON LAW & AGING, HEALTH CARE DECISION-MAKING (Feb. 27, 2019), https://www.americanbar.org/groups/law_aging/resources/health_care_decision_making.html [https://perma.cc/DZ84-DASM].

120. *Id.*

121. *Id.*; *see also* ABA COMM'N ON LAW & AGING, GUIDE FOR HEALTH CARE PROXIES TOOL #9, https://www.americanbar.org/content/dam/aba/administrative/law_aging/tool9.authcheckdam.pdf [https://perma.cc/8FRD-TUL5].

122. Frank Davies, *Living Will from Florida Goes Nationwide*, MIAMI HERALD, Oct. 23, 1998, at A8.

123. *History and Mission*, AGING WITH DIGNITY, https://www.agingwithdignity.org/about-us/history-and-mission [https://perma.cc/7CR6-JJYK].

124. *Id.*

125. AGING WITH DIGNITY, SAMPLE FIVE WISHES FORM 4 (2011), https://fivewishes.org/docs/default-source/Samples/five-wishes-sample.pdf [https://perma.cc/AZG4-FNLF].

126. *Id.* at 6–7.

127. *Id.* at 1–11.

Care and expressly convey their wishes.[128] Standard DPOA forms establish clear wishes of the individual, and specialized Health Care DPOAs are becoming more common.[129] Despite growing public discourse, only about 60% of individuals over the age of fifty have executed a living will in the United States.[130] Rates of individuals with wills vary by income and education.[131] To address these gaps, several states have recently adopted uniform DPOA statutes to complement informed consent and guardianship statutes.[132] For example, Washington State enacted the Uniform Durable Power of Attorney Act in 2016,[133] becoming the twentieth state to pass such a law.[134] The uniform acts provide default rules in case of future incapacity[135] and contain safeguards for the protection of an incapacitated principal in the medical treatment context.[136]

II. LEGAL INCAPACITY IN THE MEDICAL RESEARCH CONTEXT

Despite varied state statutes, informed consent for patients who lack capacity is fairly well settled in the clinical setting.[137] The various surrogate decision-making standards in that context—substituted judgment or best interest—are primarily focused on the benefits of treatment for, or the desires of, that particular patient.[138]

Informed consent for individuals who lack capacity in the research context, however, is much less clear. The main distinction between medical treatment and medical research is their respective purpose. The purpose of research is not necessarily to heal the patient, but rather a

128. *See* Scott, *supra* note 31, at 269.

129. *See, e.g.*, WASH. STATE HOSP. ASS'N, *supra* note 58.

130. AARP RESEARCH GRP., WHERE THERE IS A WILL . . . LEGAL DOCUMENTS AMONG THE 50+ POPULATION: FINDINGS FROM AN AARP SURVEY 2 (2000), https://assets.aarp.org/rgcenter/econ/will.pdf [https://perma.cc/KY4H-32VS].

131. *Id.* at 2–3 (noting how "[t]here is a dramatic increase in the proportion of the 50+ population having a will as household income increases from less than $15,000 annually (50% with a will) to $50,000 and over (74% with a will)" and "[p]eople with a college degree or higher levels of education are much more likely to have a will than those with a high school education or less").

132. *Power of Attorney Act*, *supra* note 23.

133. WASH. REV. CODE § 11.125.010 (2018); *see also id.* § 11.125.400.

134. *Power of Attorney Act*, *supra* note 23.

135. *Id.*

136. *See* WASH. REV. CODE § 11.125.400.

137. *See In re* Conservatorship of Groves, 109 S.W.3d 317, 328–30 (Tenn. Ct. App. 2003).

138. *See* Dippel, *supra* note 50, at 667–68.

scientific endeavor to discover and learn from the subject and his or her ailment.[139] In other words, when a patient consents to medical treatment, they are consenting to potential risks with the ultimate goal of getting better (i.e., *therapeutic*).[140] Conversely, when a patient consents to medical research, they are consenting to potential risks, with the possibility of getting better, but with the understanding that they may, in fact, get worse, and with the ultimate goal of contributing to science (i.e., *nontherapeutic*).[141]

During the informed consent process, it is critical for research participants to understand the distinction between research and treatment. This challenge, often called the "therapeutic misconception," can be heightened in research involving subjects with impaired decision-making capacity.[142] Enrollment poses its own unique challenges as well:

> Enrollment of subjects with partial impairment may require modifications to the consent form and process to enable those subjects to consent on their own behalf. When a subject's consent capacity is sufficiently impaired that the subject is unable to provide legally effective informed consent, the subject may not be enrolled unless the subject's legally authorized representative consents on the subject's behalf.[143]

Considering the history of abuse on vulnerable populations for "research purposes"—e.g., Tuskegee[144] and Nazi experimentation[145]—the global community recognizes ethical and legal standards must apply in the research context.[146] Following WWII, the Nuremburg Code

---

139. *See* Russell Korobkin, *Autonomy and Informed Consent in Nontherapeutic Biomedical Research*, 54 UCLA L. REV. 605, 611 (2007).

140. *See* Katz, *supra* note 29, at 76–77.

141. *See* Joseph L. Breault, *Protecting Human Research Subjects: The Past Defines the Future*, 6 OCHSNER J. 15 (2006); Lars Noah, *Informed Consent and The Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361 (2002).

142. *Research Involving Individuals with Questionable Capacity to Consent: Points to Consider*, NAT'L INST. HEALTH (Nov. 2009), https://grants.nih.gov/grants/policy/questionablecapacity.htm [https://perma.cc/8SSL-TTV7] [hereinafter NAT'L INST. HEALTH].

143. OFFICE OF GOOD CLINICAL PRACTICE, OFFICE OF SPECIAL MED. PROGRAMS & OFFICE OF MED. PRODS. & TOBACCO, FDA, INFORMED CONSENT INFORMATION SHEET: GUIDANCE FOR IRBS, CLINICAL INVESTIGATORS, AND SPONSORS, DRAFT GUIDANCE 35 (2014) (citing 21 C.F.R. §§ 50.3(l), 50.20 (2018)) [hereinafter FDA INFORMED CONSENT INFORMATION SHEET].

144. Sharona Hoffman, *Regulating Clinical Research: Informed Consent, Privacy, and IRBs*, 31 CAP. U. L. REV. 71, 74 (2003).

145. Peter V. Rabins, *Issues Raised by Research Using Persons Suffering from Dementia Who Have Impaired Decisional Capacity*, 1 J. HEALTH CARE L. & POL'Y 22 (1998).

146. *See* U.S. GOV'T PRINTING OFFICE, TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, at 181–82 (1949) ("1. The voluntary consent of the human subject is absolutely essential.").

established early standards.[147] In 1993, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), released international research guidelines.[148] Human subjects research standards evolved in the United States consistent with these international standards.[149]

A. Federal Regulatory and Legal Framework for Human Subjects Research

In the United States, the former Department of Health, Education, and Welfare (DHEW) first addressed the question of informed consent for those lacking decisional capacity in the research context in 1973.[150] A DHEW appointed study group published a report raising the ambiguity of consent in the research context:

> Whereas it is clear by law that consent of a parent or legal representative is valid for established and generally accepted therapeutic procedures performed on a child or an incompetent adult, it is far from clear that it is adequate for research procedures. In practice, parental or guardian consent generally has been accepted as adequate for therapeutic research, although the issue has not been definitively resolved in the courts. When research might expose a subject to risk without defined therapeutic benefit or other positive effect on that subject's well-being, parental or guardian consent appears to be insufficient.[151]

The draft also raised the concern that legal guardians might not always have the "best interest" of the patient in decision-making.[152] Because "long-term management of patients with mental disabilities is expensive and time-consuming[,]"[153] the draft speculated that a research proposal that might "reduce either the expense or the supervision

147. *Id.*

148. *See* Robert J. Levine, *New International Ethical Guidelines for Research Involving Human Subjects*, 119 ANNALS INTERNAL MED. 339 (1993).

149. *See* Joel Sparks, *Timeline of Laws Related to the Protection of Human Subjects*, NAT'L INST. HEALTH (June 2002), https://history.nih.gov/about/timelines_laws_human.html [https://perma.cc/G4G5-56SW] (discussing how from 1980 to 1983, the President's Commission's recommendations became the basis of the Common Rule, and how, in 1991, sixteen agencies adopted the Common Rule regulations).

150. Hoffmann et al., *supra* note 61, at 551.

151. Protection of Human Subjects: Policies and Procedures, 38 Fed. Reg. 31,738 (Nov. 16, 1973).

152. Hoffmann et al., *supra* note 61, at 552 n.23.

153. Protection of Human Subjects: Policies and Procedures, *supra* note 151, at 31,745.

required in caring for such persons might be appealing, whether or not there is correlative benefit to the patient."[154]

For individuals who lack capacity, the draft contemplated a supplemental model: "assent" instead of "consent."[155] Researchers may require assent when the individual has "sufficient mental competency to understand what is proposed and to express an opinion as to his or her participation."[156] After Congress abandoned the DHEW proposals, it charged later commissions with establishing principles and guidelines for "the protection of human subjects of research."[157] This work culminated in the Belmont Report in 1979.[158] Following the report's publication, the U.S. Department of Health and Human Services (HHS) promulgated regulations for research involving human subjects, known as the "Common Rule."[159] The Common Rule established guidelines for informed consent in research.[160] The regulations identify several elements required for legally effective informed consent.[161] The three main elements are: (1) information; (2) comprehension; and (3) voluntariness.[162] Importantly, the Common Rule does not contain a specific subpart governing research involving adults with impaired decision-making capacity.[163]

The National Institutes of Health (NIH) considers "consent capacity" as "an adult's ability to understand information relevant to making an informed, voluntary decision to participate in research."[164] With respect to individuals who lack consent, the NIH contemplates various scenarios impacting capacity.[165] "Impaired consent capacity may involve partial impairment, impairment that fluctuates over time, or complete impairment. For example, consent capacity can be affected by a wide

154. *Id.*

155. Hoffmann et al., *supra* note 61, at 553.

156. Protection of Human Subjects: Policies and Procedures, *supra* note 151, at 31,748.

157. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192 (Apr. 18, 1979) [hereinafter Belmont Report].

158. *Id.*

159. 45 C.F.R. § 46 (2018); Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTH CARE L. & POL'Y 88, 89 (1998).

160. 45 C.F.R. § 46.116.

161. *Id.*

162. Protection of Human Subjects: Policies and Procedures, *supra* note 151, at 31,740.

163. Stacey A. Tovino, *A "Common" Proposal*, 50 HOUS. L. REV. 787, 801 (2013); *see* 45 C.F.R. §§ 46.101–.505.

164. NAT'L INST. HEALTH, *supra* note 142.

165. *Id.*

range of disorders and conditions, such as dementia, stroke, traumatic brain injury, developmental disorders, serious mental illness, intoxication, and delirium."[166]

The leading case on informed consent in research, *Grimes v. Kennedy Krieger Institute, Inc.*,[167] involved a lead poisoning study on children in Baltimore.[168] In finding that a "special relationship" giving rise to a duty of care exists between researchers and subjects, the *Grimes* Court based their reasoning on contract law.[169] The court found that:

> [I]nformed consent agreements in nontherapeutic research projects, under certain circumstances can constitute contracts; and that, under certain circumstances, such research agreements can, as a matter of law, constitute "special relationships" giving rise to duties, out of the breach of which negligence actions may arise. . . . Additionally, we hold that *governmental regulations can create duties on the part of researchers towards human subjects out of which "special relationships" can arise*.[170]

Along with the *Grimes* decision, at least nineteen published opinions from state and federal courts recognize "the duty of researchers to secure an informed consent from research participants."[171]

1. Federal Ambiguity on Proxy Consent and the Revised Common Rule

U.S. regulations follow informed consent doctrine for surrogate decision makers.[172] Department guidance has also stated preferences on the most appropriate standard in the research context, particularly involving subjects with impaired capacity.[173] For example, NIH prefers the substituted judgment standard, in which LARs' research decisions are "guided by their knowledge of the beliefs, views, and preferences of the subject."[174] Furthermore, substituted judgment is favored "from an ethical standpoint because it is consistent with the principles of respect

166. FDA INFORMED CONSENT INFORMATION SHEET, *supra* note 143 (emphasis added).

167. 782 A.2d 807 (Md. 2001).

168. *See id.* at 811–12.

169. *Id.* at 858.

170. *Id.* (emphasis added).

171. Jon F. Merz, *The Nuremberg Code and Informed Consent for Research*, 319 J. AM. MED. ASS'N 85 (2018).

172. Elyn R. Saks et al., *Proxy Consent to Research: The Legal Landscape*, 8 YALE J. HEALTH POL'Y, L. & ETHICS 37, 44 (2008) ("The term LAR occurs in state statutes approximately 295 times.").

173. *See* NAT'L INST. HEALTH, *supra* note 142.

174. *Id.*

for persons and autonomy, which are central to informed consent."[175] NIH, however, stipulates that "[i]n the absence of knowledge of subject values, the *best interest* standard is typically used."[176]

The Belmont Report also contemplates utilizing the "best interest" standard in medical research.[177] The report states that LARs "should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interests."[178] It does, however, specify the appropriate context for applying this standard: LARs "should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest."[179]

The HHS Office of Human Research Protections (OHRP) seemingly interprets the existence of a family proxy consent to treatment statute as also authorizing proxy consent to research.[180] OHRP, therefore, defers to state statutes but has explicitly disallowed researchers to act based on statutes that allowed a non-LAR to consent.[181] On the OHRP website's Frequently Asked Questions page, the agency acknowledges that "HHS regulations are silent on the consent procedures specific to subjects with impaired decision-making capacity."[182]

In 2017, several agencies updated the Common Rule in a new Final Rule.[183] After the release of the Proposed Rule in 2011,[184] agencies received extensive public comment and several proposals to address proxy consent in research.[185] In response, the Final Rule "modified" the definition of LARs "to address jurisdictions in which no applicable law authorizes a legally authorized representative to provide consent on

175. *Id.*

176. *Id.* (emphasis added).

177. Belmont Report, *supra* note 157.

178. *Id.*

179. *Id.*

180. Saks et al., *supra* note 172, at 52.

181. *Id.* at 54–55.

182. *Informed Consent FAQs*, HHS, https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html [https://perma.cc/2HYH-8TXW].

183. *See* 45 C.F.R. § 46 (2018).

184. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 75 Fed. Reg. 44,512 (proposed July 26, 2011).

185. *See* Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,170–71; Tovino, *supra* note 163, at 787, 846–53 (proposing that "HHS amend the Common Rule to add a new Subpart E governing human subjects research involving adults with impaired decision-making capacity").

behalf of a prospective research subject."[186] The Final Rule extends the definition of LAR to "an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context."[187] Nevertheless, this change leaves considerable confusion among differing state statutes and IRB practices on proxy consent.[188] For example, the Final Rule does not define "institutional policy."[189] Ultimately, the updated Common Rule does not offer a much-needed uniform approach to proxy consent that researchers, potential subjects, and their surrogates can follow.

2. Minimal Risk Standards

Some scholars argue that nontherapeutic research involving mentally impaired subjects is legitimate only if it involves minimal risk.[190] Others, like the court in *T.D. v. New York State Office of Mental Health*,[191] hold that this type of research may not be permissible precisely because of the challenge of informed consent. The trial court stated:

> When the proposed medical course does not involve an emergency and is not for the purpose of bettering the patient's condition, or ending suffering, it may be doubtful if a surrogate decisionmaker—a guardian, a committee, a health-care proxy holder, a relative, or even a parent could properly give consent to permitting a ward to be used in experimental research with no prospect of direct therapeutic benefit to the patient himself.[192]

Either way, "a core concern a [psychiatrist] should have when a patient with AD is considering enrollment in a study is how great a risk the patient is willing to take."[193]

While ethical obligations to protect vulnerable populations from research are well-founded, a conundrum lies "[b]ecause new treatments

---

186. Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,171.

187. *Id.* at 7,260 ("If there is no applicable law . . . an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context to the subject's participation in the procedures involved in the research, will now be considered a legally authorized representative for purposes of this rule.").

188. *See* Ng Gong et al., *supra* note 28; ABA COMM'N ON LAW & AGING, *supra* note 21.

189. Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,171.

190. *See* Stacey A. Tovino, *Conflicts of Interest in Medicine, Research, and Law: A Comparison*, 117 PENN. ST. L. REV. 1291, 1316–17 (2013).

191. 690 N.E.2d 1259, 1260 (N.Y. 1997).

192. T.D. v. N.Y. State Office of Mental Health, 626 N.Y.S.2d 1015, 1020 (App. Div. 1995).

193. Edmund Howe, *Informed Consent, Participation in Research, and the Alzheimer's Patient*, 9 INNOVATIONS CLINICAL NEUROSCIENCE 47, 48 (2012).

must eventually be tested in persons suffering from the relevant condition . . . [E]xcluding incapable subjects from research would preclude the development of improved treatment for persons with serious psychiatric disorders, dementia, and other mentally debilitating conditions."[194]

Despite this dilemma, U.S. regulations adopted risk-level limitations on research. Under the Common Rule, "minimal risk" means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the routine physical or psychological examinations or tests."[195]

The *Grimes* Court acknowledged different levels of risk and prohibited proxy consent in studies with high risk.[196] The court held that "a parent . . . or other applicable surrogate, *cannot consent* to the participation of a child *or other person under legal disability* in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject."[197] Thus, *Grimes* presents a potential barrier to innovative research.

Some agencies issued clarifying guidance to establish their policy preferences on research on mentally impaired subjects that entail greater risk.[198] For example, NIH has stated that enrolling subjects with impaired decision-making capacity "is crucial to the development of new treatments and diagnostic and preventative strategies."[199] NIH further recognizes that "[r]esearch that does not directly benefit the individual subject can be of benefit to family members, other people at-risk for or with the condition, and society as a whole by advancing

194. Rebecca Dresser, *Research Involving Persons with Mental Disabilities: A Review of Policy Issues and Proposals*, *in* 1 NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY 5, 7 (1998), https://bioethicsarchive.georgetown.edu/nbac/capacity/volumeii.pdf [https://perma.cc/BHE2-DQKC].

195. 45 C.F.R. § 46.102(j) (2018).

196. Grimes v. Kennedy Krieger Inst., Inc., 782 A.2d 807, 858 (Md. 2001).

197. *Id.* (emphasis added).

198. *See, e.g.*, NAT'L INST. HEALTH, *supra* note 142 (explaining "[t]he purpose of this document is to provide investigators and [] (IRBs) with points to consider in: a) fulfilling ethical and Federal regulatory requirements to ensure the protection of the rights and welfare of research subjects who, due to impairments in their capacity to give informed consent, may be vulnerable to coercion or undue influence; and b) maintaining appropriate awareness of the ethical challenges associated with research involving this vulnerable population. Impaired decision-making capacity need not prevent participation in research, but additional scrutiny and safeguards are warranted for research involving individuals with such impairments.").

199. *Id.*

scientific knowledge of the condition or disorder."[200] In other words, research of particular diseases "may have no direct medical benefit to subjects, but will likely advance knowledge and may lead to new strategies to diagnose, treat, and prevent disease."[201]

The National Institute for Mental Health (NIMH) permits studies on mentally impaired subjects only if researchers employ an appropriate consent process.[202] The agency further stipulates that the research must involve either: (1) minimal risk, (2) greater than minimal risk but with the prospect of direct benefit to subjects, or (3) greater than minimal risk with no prospect of direct benefit to subjects but with the likelihood of gaining important knowledge about the subject's illness.[203]

a. Attitudes Towards Research with Greater Risk

In a 2000 study, researchers assessed inpatient adults at the NIH Clinical Center on research preferences in the event of future incapacity.[204] Of 2,371 adults surveyed, 11% completed a research advance directive.[205] Of these, 13% were not willing to participate in future research should they become unable to consent.[206] Conversely, 76% were willing to participate in research that might help them, but just less than half were willing to participate in research that would not help them and only posed minimal risk.[207] Finally, only 9% of those surveyed were willing to participate in research that would not help them and posed greater than minimal risk.[208] This study, however, did not focus on AD patients.[209]

A 2005 study focused on individuals with a heightened risk of AD and their thoughts about surrogate consent for research.[210] The study found that participants did express preferences among research scenarios

200. *Id.*

201. *Id.*

202. LEWIS VAUGHN, BIOETHICS: PRINCIPLES, ISSUES, AND CASES 249 (3d ed. 2017).

203. *Id.*

204. Palaniappan Muthappan, Heidi Forster & David Wendler, *Research Advance Directives: Protection or Obstacle?*, 162 AM. J. PSYCHIATRY 2389 (2005).

205. *Id.* at 2390.

206. *Id.*

207. *Id.*

208. *Id.*

209. *Id.*

210. Scott Y.H. Kim et al., *What Do People at Risk for Alzheimer Disease Think About Surrogate Consent for Research?*, 65 NEUROLOGY 1395 (2005).

of varying risks and burdens.[211] The individuals, however, were supportive of surrogate consent-based research even when risks and burdens were significant to the subjects.[212]

A more recent 2017 University of California Los Angeles (UCLA) Alzheimer's Disease Research Center (ADRC) study found similar results with AD patients ranging from normal cognition, Mild Cognitive Impairment (MCI), and clinically diagnosed dementia.[213] The UCLA study had two significant findings.[214] First, individuals with a more severe diagnosis indicated greater willingness to participate in research, regardless of risk.[215] Second, however, with greater research risk and burden, willingness to participate reduced in each diagnostic group.[216]

Therefore, the minimal risk standard remains a significant limitation on research to protect subjects who lack capacity. Individuals with AD diagnoses, however, may be more willing to participate in research with greater than minimal risk. It is important for those AD subjects to express their wishes for potential future substituted judgment.

3. Assent and Dissent Standards

The Common Rule identifies one class of vulnerable subjects with special regulations: minors.[217] These regulations set an additional standard for these subjects, who also lack the legal capacity to consent.[218] The modification afforded to minor subjects—based on the fundamental principles of patient autonomy[219]—is a requirement for "assent."[220] Assent is defined as "a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent."[221] In determining

211. *Id.* at 1395.

212. *Id.*

213. Michelle M. Nuno et al., *Attitudes Toward Clinical Trials Across the Alzheimer's Disease Spectrum*, ALZHEIMER'S RES. & THERAPY 3 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628443/pdf/13195_2017_Article_311.pdf [https://perma.cc/S6Q8-2VUJ].

214. *Id.* at 4.

215. *Id.*

216. *Id.*

217. 45 C.F.R. § 46.401–.409 (2018).

218. *Id.* § 46.408.

219. *See* Wilma C. Rossi, William Reynolds & Robert M. Nelson, *Child Assent and Parental Permission in Pediatric Research*, 24 THEORETICAL MED. & BIOETHICS 131, 132–33 (2003).

220. 45 C.F.R. § 46.408.

221. *Id.* § 46.402(b).

whether children are capable of providing assent, researchers must consider the subject's age, maturity, and psychological state.[222]

Seeking assent and respecting dissent is not legally equivalent to obtaining informed consent but maintains the dignity of all persons participating in research.[223] While regulations do not require assent for dementia research, it has been contemplated and recommended.[224] In fact, one recently published trial adopted the assent approach.[225] The trial, however, involved individuals with mild dementia and requested written consent from all trial participants.[226]

B. The Role of Institutional Review Boards

IRBs are private, independent groups that approve or deny proposed medical research.[227] The FDA defines IRBs as "any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects."[228] The purpose of IRBs role "is to assure the protection of the rights and welfare of the human subjects."[229]

Substantive legal and policy guidelines instruct investigators and IRBs on the ethical propriety of research proposals.[230] The FDA advises that IRBs and principal investigators "carefully consider" whether the participation of research subjects who lack consent capacity is "ethically appropriate and scientifically necessary."[231] The agency offers further guidance to address ethical and procedural challenges, including:

> Establishing a waiting period in the decision-making process to allow additional time for decision-making[;] [u]sing methods to enhance consent capacity, for example, through

222. *Id.* § 46.408.

223. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, FOR RESEARCHERS: NEUROSCIENCE AND CONSENT CAPACITY 5 (2015), https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/consent%20capacity%20primer%20-%20FINAL_0.pdf [https://perma.cc/Q6B2-EW9H].

224. Betty S. Black et al., *Seeking Assent and Respecting Dissent in Dementia Research*, 18 AM. J. GERIATRIC PSYCHIATRY 77 (2010); Susan Slaughter et al., *Consent and Assent to Participate in Research from People with Dementia*, 14 NURSING ETHICS 27 (2007).

225. *See* Lawrence S. Honig et al., *Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease*, 378 NEW. ENG. J. MED. 321 (2018).

226. *Id.* at 323.

227. *See* 45 C.F.R. § 46.102(g)–(h).

228. 21 C.F.R. § 56.102(g) (2018).

229. *Id.*

230. Marshall B. Kapp, *Decisional Capacity, Older Human Research Subjects, and IRBs: Beyond Forms and Guidelines*, 9 STAN. L. & POL'Y REV. 359 (1998).

231. FDA INFORMED CONSENT INFORMATION SHEET, *supra* note 143, at 35.

> (i) simplification and/or repetition of information, (ii) *involvement of a subject advocate or trusted family member/friend to assist* when sharing information about the clinical investigation . . . [and] [i]nvolving a legally authorized representative either initially or later in the clinical investigation *if consent capacity diminishes*."[232]

C. State Statutes Are Inconsistent on Proxy Consent in Research

Several state statutes contemplate proxy consent in the research context.[233] However, "[n]o state comprehensively regulates research with decisionally impaired individuals."[234] Many jurisdictions do not explicitly speak to the issue,[235] though some scholars posit that it cannot be "presumed that absence of a statute necessarily means that proxy consent to research is not permitted."[236] In other words, health care surrogate decision-making statutes could be inferred to apply in the research context.[237] Twenty-seven states have laws regarding proxy consent to research generally, though many are limited to specific types of experimental research or require court orders.[238] For example, Washington state has several statutes addressing informed consent and individuals who lack capacity,[239] yet only one explicitly mentions experimental research, and it specifically relates to nursing home patients.[240] Three states, however, explicitly prohibit or limit health care surrogates from consenting to research on behalf of the patient.[241] Some of these statutes, though, include language that allows for patients' express wishes to be upheld over the defaults.[242]

---

232. *Id.* at 36 (emphasis added).

233. Saks et al., *supra* note 172, at 46.

234. Hoffmann et al., *supra* note 61, at 550.

235. *See, e.g.*, WASH. REV. CODE § 70.70.065 (2019) (providing for surrogate consent only in the context of "health care").

236. Saks et al., *supra* note 172, at 46.

237. *Id.* at 80–84.

238. *Id.* at 42.

239. WASH. REV. CODE §§ 7.70.060, 11.88.010, 74.42.040 (2019).

240. *Id.* § 74.42.040.

241. FLA. STAT. ANN. § 765.113 (West 2019); NEV. REV. STAT. § 162A.850 (2019) ("The agent may not consent to: . . . (g) Experimental medical, biomedical or behavioral treatment, or participation in any medical, biomedical or behavior research program."); N.H. REV. STAT. ANN. § 137-J:5 V(d) (2019) ("Nothing in this chapter shall be construed to give an agent or surrogate authority to . . . [c]onsent to . . . experimental treatment of any kind.").

242. *See, e.g.*, FLA. STAT. ANN. § 765.113(1) ("Unless the principal expressly delegates such authority to the surrogate in writing . . . a surrogate or proxy may not provide consent

1. Specialized State Statutes

In 2002, California passed a law explicitly allowing proxy consent for research.[243] The legislature passed the law partly in response to a UCLA moratorium on approval of human subjects research involving decisionally-impaired participants unless a court-appointed conservator obtained consent.[244] UCLA made this decision due to the lack of certainty or guidance on surrogate consent to research.[245]

The California law restricts proxy consent to medical experiments that *relate* to the cognitive impairment or lack of capacity of the research participants.[246] This would likely include AD research. Further, the law prioritizes the "substituted judgment" decision-making standard but allows for "best interest" standard when patient wishes are unknown.[247] To avoid decisions based solely on minimal risk, the law specifies "[i]n determining the person's best interest, the decisionmaker shall consider the person's personal values and his or her best estimate of what the person would have chosen if he or she were capable of making a decision."[248]

Several other states followed California's model.[249] Kansas has a specific provision allowing proxy consent, although it is restricted to IRB-approved research protocols and prohibits consent if contrary to the incompetent patient's permission, expressed orally or in writing.[250] New Jersey also limited proxy consent to IRB-approved and monitored research, as well as certain benefit/risk criteria.[251]

Conversely, many states restrict surrogate health care decision-making to specific decisions. For example, North Carolina's living will statute limits proxy consent to the withholding or withdrawing of life-

---

for . . . experimental treatments that have not been approved by a federally approved institutional review board.").

243. 2002 Cal. Legis. Serv. 477 (West) (codified at CAL. HEALTH & SAFETY CODE § 24178 (West 2019)).

244. Saks et al., *supra* note 172, at 40–41.

245. *Id.*

246. CAL. HEALTH & SAFETY CODE § 24178.

247. *Id.* § 24178(g).

248. *Id.*

249. *See* KAN. STAT. ANN. § 65-4974 (West 2019) (specialized provision applicable only to consent in medical research); N.J. STAT. ANN. § 26:14-5 (West 2019); OKLA. STAT. ANN. tit. 63, § 3102A (West 2019).

250. KAN. STAT. ANN. § 65-4974.

251. N.J. STAT. ANN. § 26:14-5.

prolonging measures.[252] Many jurisdictions follow this approach—perhaps in response to *Cruzan*—continuing to focus health care surrogate decision-making on end-of-life decisions, like withholding or withdrawing life-sustaining treatments, instead of contemplating participation in medical research.[253] As UCLA identified almost two decades ago, a lack of clear guidance for researchers and research institutions concerning proxy consent remains a challenge. Given the trend of subjects traveling to institutions in different jurisdictions to participate in the limited number of AD clinical trials available, the inconsistency in state laws may pose a threat not only to trial enrollment, but also to advancements in science.[254]

2. Research Advance Directives

Several proposed guidelines, including at the state level, suggest requiring competent individuals to document their preferences in a formal advanced directive.[255] Utah has the only living will statute that explicitly mentions research.[256] Utah allows advance health care directive documents to "authorize an agent to consent to the adult's participation in medical research."[257]

In the 2000 NIH study, researchers assessed how the proposed requirement might affect research by counting how many adults completed research advance directives.[258] Of 2,371 adults surveyed, 11%

---

252. N.C. GEN. STAT. § 90-322 (2019).

253. *See, e.g.*, CONN. GEN. STAT. ANN. §§ 19a-570–571 (West 2019); IOWA CODE ANN. § 144A.7 (West 2019); MONT. CODE ANN. § 50-9-106 (West 2019); OHIO REV. CODE ANN. § 2133.08 (West 2017); VT. STAT. ANN. tit. 18, § 9731 (West 2019) (limited to making decisions about DNR orders or Clinician Orders for Life-Sustaining Treatment).

254. *Compare Search of: Recruiting Studies | Alzheimer's Disease*, CLINICALTRIALS.GOV (Mar. 9, 2018), https://clinicaltrials.gov/ct2/results/map?recrs=a&cond=Alzheimer+Disease&map= [https://perma.cc/J359-UKW8] (223 AD trials currently recruiting in the United States; 395 AD trials currently recruiting globally), *with Search of: Recruiting Studies | Breast Cancer*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results/map?recrs=a&cond=Breast+Cancer&map= [https://perma.cc/QJ6L-P8LL] (936 breast cancer trials currently recruiting in the United States; 1,784 breast cancer trials globally).

255. *See* Dresser, *supra* note 194; Valerie Gutmann Koch, *A Policy in Flux: New York State's Evolving Approach to Human Subjects Research Involving Individuals Who Lack Consent Capacity*, 42 J.L. MED. & ETHICS 383, 384 (2014) (New York State Advisory Work Group formed in response to the *T.D.* litigation); Franklin G. Miller, *Comments on the Second Report of the Maryland Attorney General's Research Working Group*, 1 J. HEALTH CARE L. & POL'Y 193 (1998).

256. UTAH CODE ANN. § 75-2a-107(1)(a)(v) (West 2019).

257. *Id.*

258. Muthappan et al., *supra* note 204.

had completed a research advanced directive.[259] The study concluded that research-specific advance directives might block important research.[260] The study did not, however, focus on individuals with AD, which is degenerative, fatal, and currently has no prevention, treatment, or cure.[261]

III. THE STATE OF ALZHEIMER'S DISEASE RESEARCH

AD presents a global public health crisis; it cannot be prevented, treated, or cured. This Part examines the current state of AD in the United States and the history of AD research failures. It also explores attitudes towards AD research, which are mostly favorable. Finally, it offers an overview of how researchers assess consent capacity for the few AD clinical trials currently available.

A. Alzheimer's Disease Is an Emerging Public Health Crisis

An estimated 5.5 million individuals in the United States are currently living with AD.[262] By 2050, this number could rise as high as 16 million.[263] AD is the sixth leading cause of death in the United States.[264] It kills more than breast cancer and prostate cancer combined.[265] Technically, physicians cannot definitively diagnose AD until an autopsy is conducted after death.[266] Physicians, however, have devised neurological assessments to determine whether patients likely have progressive AD.[267] This process typically begins with a diagnosis

259. *Id.*

260. *Id.*

261. Alzheimer's Ass'n, *supra* note 3, at 326, 329.

262. *Id.* at 334 ("Alzheimer's dementia is underdiagnosed and underreported.").

263. *Id.* at 338.

264. *Id.*

265. *Id.*

266. *How Is Alzheimer's Disease Diagnosed?*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/how-alzheimers-disease-diagnosed [https://perma.cc/N6JR-SGZH] ("It's important to note that Alzheimer's disease can be *definitively* diagnosed only after death, by linking clinical measures with an examination of brain tissue in an autopsy. Occasionally, biomarkers—measures of what is happening inside the living body—are used to diagnose Alzheimer's.").

267. *See* Jacqueline K. Kueper et al., *The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review*, 63 J. ALZHEIMER'S DISEASE 423 (2018).

of "mild cognitive impairment" (MCI).[268] MCI generally refers to dementia, delirium, or another cognitive syndrome.[269] Because AD symptoms are not always readily recognizable, especially for unsuspecting patients (e.g., "early onset" patients under age sixty-five), patients may be misdiagnosed or undiagnosed until mid-stage symptoms appear.[270]

Beyond the physical cost, AD causes tremendous emotional strain and financial expense.[271] In 2017, Alzheimer's and other dementias cost the nation $259 billion.[272] More than 16 million people provide unpaid care for individuals with AD or other dementias.[273] These caregivers provide an estimated 18.2 billion hours of care valued at more than $230 billion.[274]

Recognizing the catastrophic costs, Congress passed NAPA in 2011 to coordinate all federal AD initiatives.[275] The statute also created the National Alzheimer's Project under HHS.[276] Subsequently, Congress increased funding for AD research through the NIH.[277] Despite exponential funding surges, the U.S. government funds only one third of the AD clinical trials currently recruiting in the United States.[278]

---

268. *See What Is Mild Cognitive Impairment?*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/what-mild-cognitive-impairment [https://perma.cc/GM7J-JWNF].

269. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (DSM-IV) 123–24 (4th ed. 1994).

270. *See* Alzheimer's Ass'n, *supra* note 3, at 334, 370 n.A4, 371.

271. *See* Freeman, *supra* note 6.

272. Alzheimer's Ass'n, *supra* note 3 (Medicare: $131 billion; Medicaid: $44 billion; out of pocket: $56 billion; other: $28 billion).

273. *Id.*

274. *Id.*

275. National Alzheimer's Project Act, Pub. L. No. 111-375, 124 Stat. 4100 (codified at 42 U.S.C. § 11225 (2018)). The statute designates the Secretary of Health and Human Services as the implementer of an integrated national plan and coordinator of Alzheimer's research and services across all federal agencies. 42 U.S.C. § 11225; *see also id.* § 11201 (providing statistics illustrating Congress's findings).

276. 42 U.S.C. § 11225(b).

277. Consolidated Appropriations Act, 2017, Pub. L. No. 115-31, 131 Stat. 525 ($2,048,610,000 for the National Institute on Aging); *see also* OFFICE OF MGMT. & BUDGET, BUDGET OF THE U.S. GOVERNMENT FISCAL YEAR 2017, at 11 (2016) ("A seven percent increase in National Institutes of Health . . . will go toward critical research priorities like Alzheimer's disease.").

278. *Search of: Recruiting Studies | Alzheimer's Disease | NIH, U.S. Fed*, CLINICALTRIALS.GOV (May 13, 2019), https://clinicaltrials.gov/ct2/results/map?recrs=a&cond=Alzheimer+Disease&fund=01&map= [https://perma.cc/5X7X-GBM3] (discussing how the NIH and other U.S. federal agencies fund seventy-three AD trials currently recruiting); *see also Search of: Recruiting Studies | Alzheimer's Disease*, *supra* note 254 (223 AD trials currently recruiting in the United States).

B. Alzheimer's Research: A History of Failure

Despite the time, effort, and increasing resources, researchers have not achieved a serious breakthrough in AD research.[279] In the past several decades,[280] AD research has seen a remarkable 99.6% failure rate.[281] From 2002 to 2012, researchers conducted clinical trials with 244 drugs for AD.[282] Only one of the 244 drugs successfully completed clinical trials and went on to receive FDA approval.[283]

While the leading theory of the disease identifies beta-amyloid protein as a key component of the disease,[284] researchers have failed to effectively target amyloid or other AD-specific traits.[285] In other words, without fully understanding how AD works, researchers struggle to identify a drug agent that affects the progression of the disease.[286] Furthermore, experts have identified several other factors to account for these failures, including the "high cost of drug development" and the blood-brain barrier, "which only very specialized small-molecule drugs can cross."[287]

NIH Director Dr. Francis Collins, testifying before the U.S. Senate Appropriations Subcommittee on Labor, Health and Human Services in February 2014, stated that "[w]e are not at the moment limited by ideas. We're not limited by scientific opportunities. We're not limited by talent. We are, unfortunately, limited by resources to be able to move this enterprise forward at the pace that it could take."[288]

---

279. Freeman, *supra* note 6.

280. Carroll, *supra* note 13; Freeman, *supra* note 6; Healy, *supra* note 13 ("Idalopirdine, an experimental drug that seemed one of the most promising candidates to treat Alzheimer's disease, failed several phase 3 clinical trials.").

281. Burke, *supra* note 13.

282. Alzheimer's Ass'n, *supra* note 3, at 332 (based on trials registered with a NIH registry of publicly and privately funded clinical studies).

283. *Id.*

284. *Id.* at 328–29.

285. *See* Adam Feuerstein, *Biogen Halts Studies of Closely Watched Alzheimer's Drug, A Blow to Hopes for New Treatment*, SCIENTIFIC AM.: STAT (Mar. 22, 2019), https://www.scientificamerican.com/article/biogen-halts-studies-of-closely-watched-alzheimers-drug-a-blow-to-hopes-for-new-treatment/ [https://perma.cc/3Z39-JQN6].

286. Alzheimer's Ass'n, *supra* note 3, at 328 ("[M]uch is yet to be discovered about the precise biological changes that cause the disease, why it progresses more quickly in some than in others, and how the disease can be prevented, slowed or stopped.").

287. *Id.* at 332.

288. *Taking a Toll on Families and the Economy: The Rising Cost of Alzheimer's in America: Hearing Before the Subcomm. on Dep'ts. of Labor, Health & Human Servs., & Educ., & Related Agencies of the S. Comm. on Appropriations*, 113th Cong. 19 (2014) [hereinafter *Taking a Toll*] (statement of Francis Collins, Director, National Institutes of Health).

Congress responded to Dr. Collins's plea with annual appropriations increases directed to AD research.[289] However, researchers and funders continue to focus on studying the basic science behind AD.[290] Therefore, as opposed to investing in so-called "ideas" and "talent" towards a cure, research is focusing precious dollars on the basic questions that may not impact for patients for at least another generation.[291]

Despite a few promising studies,[292] the current research strategy focuses on prevention and treating symptoms.[293] The medical community still does not fully know what causes cancer, but thanks to aggressive and deliberate clinical trials, we have treatments and even cures for most cancers.[294] Unsurprisingly, there are approximately 1,800 currently recruiting cancer clinical trials compared to fewer than 400 AD clinical trials.[295] Only seventeen of AD trials in the final stage of drug development tested disease-modifying therapies in 2018.[296] In other

289. *See* Richard Hodes, *We Have a Budget for FY 2019!*, NAT'L INST. ON AGING (Oct. 24, 2018), https://www.nia.nih.gov/research/blog/2018/10/we-have-budget-fy-2019 [https://perma.cc/ZQ47-VYY9] ("The biggest increases in funding directed at Alzheimer's and related dementias came from Congress in the last four fiscal years: additional appropriations in FY 2016 reached $350 million; in FY 2017, $400 million; in FY 2018, $414 million; and this year's additional funding of $425 million. Overall, between FY 2014 and 2019, NIA funding increases for Alzheimer's disease and related dementias research totaled $1.7 billion.").

290. *See* Robert Preidt, *The Focus Shifts in Alzheimer's Research*, HEALTHDAY NEWS (Apr. 10, 2018), https://consumer.healthday.com/cognitive-health-information-26/alzheimer-s-news-20/the-focus-shifts-in-alzheimer-s-research-732767.html [https://perma.cc/HR7K-VBBH].

291. *See Taking a Toll*, *supra* note 288.

292. *See, e.g.*, Jeff D. Williamson et al., *Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial*, 321 J. AM. MED. ASS'N 553, 559 (2019) (stating "[t]his is the first trial, to our knowledge, to demonstrate an intervention that significantly reduces the occurrence of MCI . . . [h]owever, some caution should be exercised in interpreting this result, both because MCI was not the primary cognitive outcome of the trial and because it is not clear what this effect may mean for the longer-term incidence of dementia." Notably, this study concluded that treating adults with more aggressive blood pressure control "did not result in a significant reduction in the risk of probable dementia").

293. *See, e.g.*, *U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (POINTER)*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT03688126 [https://perma.cc/5VNC-LMG6] ("The purpose of this research study is to see if lifestyle changes can protect memory and thinking (cognition) as we age. A recent study in Finland found that a combination of physical and cognitive exercise, diet, and social activity protected cognitive function in healthy older adults who were at increased risk of significant memory loss. So far no medications can rival this positive outcome. The point of POINTER is to test if lifestyle change can also protect against memory loss in Americans.").

294. *See* Ron Louie, *Alzheimer's Clinical Research Lacks Leadership*, BALT. SUN (Apr. 26, 2017, 2:16 PM), https://www.baltimoresun.com/news/opinion/oped/bs-ed-alzheimer-progress-20170426-story.html [https://perma.cc/Q22H-F93B].

295. *See supra* note 254.

296. *See* Jeffrey Cummings et al., *Alzheimer's Disease Drug Development Pipeline: 2018*, 4 ALZHEIMER'S & DEMENTIA 195–96 (2018) ("Phase III of the 2018 AD pipeline has 26 agents; 17

words, if informed consent remains a barrier to more aggressive clinical trials, AD research may continue to stall as a result.

1. Attitudes Toward Proxy Consent for Alzheimer's Research

As mentioned in Part II, researchers conducted several studies regarding older adults and AD patients' attitudes towards research and future incapacity.[297] A 2002 NIH study assessed attitudes of healthy individuals who had a family history of AD or prior research participation.[298] The study found that "[t]he vast majority of respondents were willing to participate in clinical research" if their ability to consent became impaired.[299] A 2009 national study explored older adults' attitudes toward enrollment of incompetent subjects in AD research.[300] A vast majority of adults surveyed over sixty-five years of age indicated that they would be willing to give advanced consent to "blood draw studies" and almost half said they would be willing to participate in studies that included lumbar punctures, which may cause pain.[301] These findings suggest that not offering higher risk studies for AD patients would in fact "*disrespect* these patients."[302]

Another study found that while there is general support for proxy consent in AD research, surrogates may prefer the best interest standard.[303] Surrogate decision makers surveyed may want to maximize what they think is best, as opposed to pursuing what they believe the patients would want.[304] In other words, many study partners may be compelled to impose the best interest standard instead of substituted judgment. Regardless of the standard, the study found that AD patients

---

[disease-modifying therapies], one cognitive-enhancing agent, and eight drugs for behavioral symptoms. Among the [disease-modifying therapies], 14 addressed amyloid targets, one involved a tau-related target, one involved neuroprotection, and one had a metabolic [mechanism of action].").

297. *See supra* Section II.A.2.a.

298. Dave Wendler et al., *Views of Potential Subjects Toward Proposed Regulations for Clinical Research with Adults Unable to Consent*, 159 AM. J. PSYCHIATRY 585 (2002).

299. *Id.* at 589.

300. Jason Karlawish et al., *Older Adults' Attitudes Toward Enrollment of Non-Competent Subjects Participating in Alzheimer's Research*, 166 AM. J. PSYCHIATRY 182 (2009).

301. *Id.*

302. Howe, *supra* note 193, at 48 (emphasis added).

303. Jason Karlawish et al., *The Views of Alzheimer Disease Patients and Their Study Partners on Proxy Consent for Clinical Trial Enrollment*, 16 AM. J. GERIATRIC PSYCHIATRY 240, 245 (2008) ("[M]ost proxies favored the bests interest over the substituted judgment standard to guide making decisions about study participants.").

304. *Id.*

and their study partners supported proxy consent for themselves and as a matter of policy.[305]

C. Assessing Capacity to Consent in Alzheimer's Research

As a disease that slowly cripples mental capacity over an extended period, AD presents a unique challenge in clinical trials. One of the most pervasive legal doctrines present in medical and research settings is informed consent.[306] This challenging legal and regulatory mandate becomes more complicated with patients who lack the capacity to consent.[307] While there may be a distinction between "capacity" and "competency," the terms are used interchangeably for medical and legal purposes.[308]

The first threshold question is whether an individual has the capacity to consent. Does an AD diagnosis immediately equate to lack of capacity? If the patient is in an early AD stage at diagnosis, they may be deemed "competent" to sign an advance directive, a DPOA for health care, and perhaps, a research consent form.[309] As the disease progresses, the window of opportunity closes, and the question becomes much more difficult. If the patient has not implemented an advance directive or DPOA and a clinical trial becomes available for later stage AD patients, how can they enroll? Clinically, "patients with Alzheimer's disease and other dementias have high rates of incompetence with regard to such decisions; more than half of patients with mild-to-moderate dementia may have impairment, and incompetence is universal among patients with more severe dementia."[310]

Clinicians have contemplated how to assess and determine capacity to consent,[311] specifically for patients with dementia or AD. Study results raised the concern that many patients with mild AD may not be competent to consent to treatment and supported the value of

---

305. *Id.*

306. *See supra* Section I.A.

307. *See supra* Section I.A.

308. *See, e.g.*, Dippel, *supra* note 50; *cf.* Hoffman et al., *supra* note 61; Saks et al., *supra* note 172.

309. *See supra* Section I.B.2.

310. Paul S. Appelbaum, *Assessment of Patients' Competence to Consent to Treatment*, 357 NEW ENG. J. MED. 1834, 1835 (2007) (citing Scott Y. H. Kim, Jason H. Karlawish & Eric D. Caine, *Current State of Research on Decision-Making Competence of Cognitively Impaired Elderly Persons*, 10 AM. J. GERIATRIC PSYCHIATRY 151 (2002)).

311. Evan G. DeRenzo, Robert R. Conley & Raymond Love, *Assessment of Capacity to Give Consent to Research Participation: State-of-the-Art and Beyond*, 1 J. HEALTH CARE L. & POL'Y 66 (1998).

standardized clinical vignettes for assessment of competency in dementia.[312] For example, the "Alzheimer's Disease Assessment Scale-Cognitive" subscale "is the *de facto* standard primary outcome neuropsychological measure for AD trials."[313] It measures several cognitive domains, including memory, language, and praxis.[314] There remains, however, no standardized assessment tool nor ethical or regulatory framework to determine an AD patient's ability to consent.

IV. UNIFORM PROXY CONSENT STANDARDS ARE NEEDED FOR RESEARCH SUBJECTS WITH ALZHEIMER'S DISEASE

While the updated Common Rule superficially solves the problem of proxy consent in research, it ultimately leaves confusion among differing state statutes and IRB practices.[315] Indeed, most states have enacted laws to address surrogate decision-making in clinical contexts.[316] According to the updated Common Rule, these laws can simply be extended to the research context.[317] However, this quick fix could have negative consequences on AD research, especially in states that restrict surrogate decision-making and follow the "best interest" standard. Therefore, this Part argues that despite the Common Rule update, states should enact laws for proxy consent in research that explicitly apply the substituted judgment standard. Furthermore, IRBs and researchers should consider modifications to the informed consent process, including respecting assent and dissent for subjects with AD to enhance research participation.

A. States Should Adopt Laws to Explicitly Address Surrogate Decision-Making in Research

Fewer than a dozen states have contemplated proxy consent to make decisions about enrollment in medical research.[318] State silence on this

312. Daniel C. Marson et al., *Assessing the Competency of Patients with Alzheimer's Disease Under Different Legal Standards*, 52 ARCHIVES NEUROLOGY 949, 949 (1995).

313. Kenneth Rockwood et al., *The Clinical Meaningfulness of ADAS-Cog Changes in Alzheimer's Disease Patients Treated with Donepezil in an Open-Label Trial*, 7 BMC NEUROLOGY 26, 26 (2007) (emphasis in original).

314. *Id.*

315. ABA COMM'N ON LAW & AGING, *supra* note 21; Ng Gong et al., *supra* note 28.

316. ABA COMM'N ON LAW & AGING, *supra* note 21.

317. Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,260.

318. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 223. For a discussion of the various state statutes, see Saks et al., *supra* note 172 and Section II.C.1, *supra*.

issue forced the federal government, as well as private institutions and IRBs, to fill the gaps. The result has been ill-defined policies regulating research involving participants who lack capacity.[319]

Government agencies and commentators widely recognize the lack of clear guidance on surrogate decision-making in research.[320] For example, Bioethics.gov states: "Although OHRP guidance indicates that state laws about appointing LARs for medical care might be relevant, uncertainty remains regarding whether laws specific to medical decision can or should extend to research decisions."[321] Even though the 2017 Common Rule update does extend LARs for medical decisions to research,[322] the question remains whether they *should*. Considering the wide variety in state law standards and IRB practices,[323] the need for uniformity and certainty remains.

To resolve this uncertainty, states should amend their current health care surrogate decision-maker laws to include a provision explicitly addressing participation in research. Amendments of this kind would clarify LARs decision-making parameters in the research context. Alternatively, states could follow California, Oklahoma, Kansas, and New Jersey by enacting specialized statutes to grant proxy consent in medical research.[324] Additionally, these statutes might influence lawyers to advise their clients to contemplate the possibility of participating in research and include their preferences in advance directives. Default DPOA for Health Care and living will forms may follow to include provisions for individuals to consider proxy consent in research.

1. The Substituted Judgment Standard Is More Appropriate than the Best Interest Standard in Alzheimer's Research

If states adopt LAR decision making in research laws, they should follow the substituted judgment standard. Currently, states vary widely on which standard surrogate decision-makers should follow—substituted judgment, best interest, or both.[325] The 2017 Common Rule update overlooked this potential problem, as the regulatory change extends

319. Scott Y. H. Kim, *The Ethics of Informed Consent in Alzheimer Disease Research*, 7 NAT'L REV. NEUROLOGY 410 (2011).

320. *See* PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 223, at 7.

321. *Id.*

322. Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,260.

323. ABA COMM'N ON LAW & AGING, *supra* note 21; Ng Gong et al., *supra* note 28.

324. *See supra* notes 243, 249 and accompanying text.

325. *See* Frolik & Whitton, *supra* note 68; Saks et al., *supra* note 172.

these various surrogate decision-making standards to the research context.[326] Despite the difficulties of obtaining informed consent from subjects with AD, there is increasing evidence that such individuals and their surrogates can make decisions about research participation that are consistent with the subject's values.[327] Because substituted judgment—or at least a hybrid model[328]—is ideal for AD research,[329] any amendments or statutes for surrogate decision-making in research must articulate this standard clearly, while distinguishing standards for medical treatment.

If researchers and surrogates adopt a "best interest" standard for decision making in AD clinical trials, LARs might dictate AD subject enrollment or non-enrollment.[330] For example, LARs might make decisions based on what they think is best for their loved ones, or worse, on LARs' own personal desires and preferences.[331] This approach, therefore, could result in a chilling effect on Alzheimer's research enrollment—particularly in studies for later stage subjects that go beyond "minimal risk."

A substituted judgment approach would instead focus on the subject's preferences.[332] Whether the subject stated their wishes officially in an advanced directive or expressed their attitudes towards research throughout their life, LARs and researchers should abide by the subject's wishes. Upon diagnosis of AD, patients likely maintain decision-making capacity to sign an advanced directive and express their desire to enroll in a clinical trial should the opportunity arise after they lose capacity. Therefore, physicians, social workers, and other care team members should recommend that newly diagnosed AD patients consider research participation in an advanced directive. Researchers must honor advance directives when they are in place and encourage subjects to develop directives in the event that participants might lose capacity during the course of a study.[333] If the subject does not have an advanced directive in place, a clear state statute outlining LAR decision-making in research would enable subjects to enroll.

---

326. Federal Policy for the Protection of Human Subjects, *supra* note 25, at 7,170–71.

327. Kim, *supra* note 319.

328. Frolik & Whitton, *supra* note 68.

329. NAT'L INST. HEALTH, *supra* note 142.

330. Karlawish et al., *supra* note 303, at 246.

331. *Id.* at 240.

332. *See supra* Sections I.B.1.a (discussing substituted judgment standard), III.B.1 (reviewing positive attitudes towards participation in AD research).

333. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 223, at 2.

B. Modifying the Informed Consent Process Might Enhance Alzheimer's Research Participation

Informed consent can be an overwhelming and complicated process. Physicians and researchers must inform prospective medical research participants of the risks and benefits of research,[334] which might consist of a long document with complex medical terminology. The assumption that even fully competent subjects understand this complex information is highly suspect. Therefore, various entities have made recommendations to simplify the process with the goal of enhancing understanding. "An individual's understanding of the information needed to make a decision depends in part on how the information is presented and explained."[335]

With AD patients and their surrogates, consent information must explain the difference between therapeutic and non-therapeutic research. Researchers must also ensure that subjects understand the expected levels of burden and risk. IRBs, on the other hand, should not automatically disapprove proposals that might pose greater than minimal risk.[336] Certain AD patients may be willing to participate in these studies, which may be necessary for progress towards NAPA's goal to treat and prevent AD by 2025.[337]

1. Respecting Assent and Dissent in Alzheimer's Research

The ethical underpinnings of informed consent are the right to autonomy and individual rights. To achieve these fundamental goals, AD clinical trials should adopt an assent standard for individuals with some capacity. While advance directives expressing research wishes would certainly provide clear and convincing evidence that a subject agrees to participate in studies broadly, they may not express a wish to participate in a particular study. Therefore, IRBs and principal investigators should consider assent and dissent as a supplemental model. "Many participants lacking consent capacity can still express meaningful desires regarding research procedures."[338] Seeking assent and respecting dissent maintains the dignity of all persons participating

---

334. *Id.*

335. *Id.* at 6.

336. *See* Ng Gong et al., *supra* note 28.

337. National Alzheimer's Project Act, Pub. L. No. 111-375, 124 Stat. 4100 (codified at 42 U.S.C. § 11225 (2018)).

338. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 223, at 6.

in research.[339] Furthermore, "[m]eaningful expressions of assent and dissent are salient, even if insufficient, evidence of participants' perspectives regarding decisions made on their behalf."[340] LARs will, of course, maintain control over signing informed consent forms, but this must not preclude investigators from respecting subjects' assent and dissent to participation.

As discussed in Part II, researchers conducting clinical trials involving another population with diminished capacity—children—have widely adopted assent. While children do not have the legal authority to consent, regulations recognize the subject's autonomy and their right to be included in the decision-making process.[341] It follows that adult subjects with diminished capacity must have a role in the informed consent process. Principal investigators must respect incapacitated subjects' assent and dissent to participate in clinical trials.[342]

An outstanding challenge with this approach is the unpredictability of Alzheimer's disease and its progression. The challenge beyond subjects providing adequate informed and voluntary consent to participate in a study is the subsequent likelihood that they will lose their capacity for independent choice.[343] "As a result, they become unable to exercise their right to withdraw from a study. Study designs must, therefore, provide for this contingency."[344]

CONCLUSION

The National Alzheimer's Project Act's ambitious goal to "prevent and effectively treat" AD by 2025 has a rapidly approaching deadline.[345] In order to come remotely close to achieving NAPA's goals, researchers must develop clinical trials, perhaps with greater than minimal risk, for individuals with later stage AD. Establishing a uniform standard for surrogate decision making and proxy consent in research will promote AD patients' autonomy to participate in critical clinical trials. Because the federal government failed to establish such an approach in the 2017

339. *Id.*

340. *Id.*

341. 45 C.F.R. § 46.402(b) (2018).

342. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 223.

343. NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY ch. 2 (1998), https://bioethicsarchive.georgetown.edu/nbac/capacity/Informed.htm [https://perma.cc/S6E3-BU46].

344. *Id.*

345. National Alzheimer's Project Act, Pub. L. No. 111-375, 124 Stat. 4100 (codified at 42 U.S.C. § 11225 (2018)).

Common Rule update—leaving the question of proxy consent in research to a variety of state laws and IRB practices—states must adopt clear research-specific proxy consent statutes. Applying the substituted judgment standard instead of the best interest standard for surrogate decision making in the research context will ensure a more accurate and respectful approach. Finally, respecting subjects' autonomy, even after they are deemed incompetent, by adopting assent and dissent standards is consistent with regulations for minors and other vulnerable populations. With a uniform approach to proxy consent in research, AD patients, families, surrogates, and researchers will know what to expect in their collective goal to find a cure.