



**REPORT AND RECOMMENDATIONS
FOR RESEARCH WITH HUMAN SUBJECTS
WHO LACK CONSENT CAPACITY**

New York State Task Force on Life and the Law

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Members of the New York State Task Force on Life and the Law

Nirav R. Shah, M.D., M.P.H.

Commissioner of Health, New York State

Karl P. Adler, M.D.

Cardinal's Delegate for Health Care, Archdiocese of NY

Donald P. Berens, Jr., J.D.

Former General Counsel, New York State Department of Health

Rabbi J. David Bleich, Ph.D.

Professor of Talmud, Yeshiva University, Professor of Jewish Law and Ethics, Benjamin Cardozo School of Law

Rock Brynner, Ph.D., M.A.

Professor and Author

Karen A. Butler, R.N., J.D.

Partner, Thuillez, Ford, Gold, Butler & Young, LLP

Carolyn Corcoran, J.D.

Principal, James P. Corcoran, LLC

Nancy Neveloff Dubler, LL.B.

Consultant for Ethics, NYC Health & Hospitals Corp., Professor Emerita, Albert Einstein College of Medicine

Paul J. Edelson, M.D.

Adjunct Professor of Clinical Pediatrics, College of Physicians and Surgeons, Columbia University

Joseph J. Fins, M.D., M.A.C.P.

Chief, Division of Medical Ethics, Weill Medical College of Cornell University

Rev. Francis H. Geer, M.Div.

Rector, St. Philip's Church in the Highlands

Samuel Gorovitz, Ph.D.

Professor of Philosophy, Syracuse University

Cassandra E. Henderson, M.D., C.D.E., F.A.C.O.G.

Director of Maternal Fetal Medicine, Lincoln Medical and Mental Health Center

Hassan Khouli, M.D., F.C.C.P.

Chief, Critical Care Section, St. Luke's – Roosevelt Hospital

Rev. H. Hugh Maynard-Reid, D.Min., B.C.C., C.A.S.A.C.

Director, Pastoral Care, North Brooklyn Health Network, New York City Health and Hospitals Corporation

John D. Murnane, J.D.

Partner, Fitzpatrick, Cella, Harper & Scinto

Samuel Packer, M.D.

Chair of Ethics, North Shore-LIJ Health System

Robert Swidler, J.D.

VP, Legal Services, St. Peter's Health Partners

Sally T. True, J.D.

Partner, True and Walsh, LLP

Task Force on Life and the Law Staff

Stuart C. Sherman, J.D., M.P.H.

Executive Director

Susie A. Han, M.A., M.A.

Deputy Director, Principal Policy Analyst

Valerie Gutmann Koch, J.D.

Senior Attorney

Angela R. Star

Administrative Assistant

Acknowledgements

This report presents and assesses legal and ethical considerations, identifies policy options, and makes recommendations regarding the conduct of human subjects research involving adults who lack consent capacity in New York State. Although research involving adults lacking consent capacity is permitted in New York State, until recently it was limited because of uncertainty about who could provide surrogate consent to participate. In 2010, a new State law, the Family Health Care Decisions Act, changed the legal landscape by permitting surrogate consent to health care and potentially opened up the field of research requiring surrogate consent. However, there remain few rules and little guidance to ensure that there is consistently ethical conduct of research involving adults lacking consent capacity. An underlying goal of this work is to ensure that research protocols are available to all, so that individuals who lack consent capacity may realize the benefits of research and share its risks and burdens as their non-cognitively impaired peers, while also ensuring the appropriate level of protections.

In light of these goals, this *Report and Recommendations for Research with Human Subjects who Lack Consent Capacity* provides guidance and best practices that will assist institutions, institutional review boards, researchers, and surrogate decision-makers in the ethical conduct of research involving adults who lack the capacity to consent.

The participation of clinicians, researchers, and government officials was critical to the deliberations of the Task Force. For their formal presentations and participation in meetings with the Task Force, we thank Paul Appelbaum, David Strauss, Jonathan Karmel, and Tony Watson.

We also thank former Task Force legal and policy interns and fellows Brendan Parent, Nicole Naudé, Apoorva Ambavane, and Daniel Marcus-Toll for their hard work.

Finally, we would like to gratefully acknowledge the work of former Task Force staff members who contributed to this report. Former Executive Directors Tia Powell and Beth Roxland, who initiated and moved the report forward, respectively, were instrumental in its evolution. The Task Force thanks Carrie Zoubul, who served as the Senior Attorney during a large portion of the research and writing of this project.

The Task Force's previous reports and proposals have informed and focused public debate and have served as a catalyst for broad consensus within New York State. The Task Force hopes that these recommendations will achieve the same goals.

Sincerely,

Susie A. Han, M.A., M.A.
Deputy Director

Valerie Gutmann Koch, J.D.
Senior Attorney

On behalf of the New York State Task Force on Life and the Law

From the Executive Director

The New York State Task Force on Life and the Law (Task Force) was established in 1985 by Governor Mario Cuomo to assist the State in developing public policy on issues arising at the interface of medicine, law, and ethics. The Task Force is chaired by the Commissioner of Health, and consists of approximately 23 Governor-appointed experts who volunteer their time. The Task Force is comprised of leaders in the fields of religion, philosophy, law, medicine, nursing, and bioethics, and is chaired by New York State's Commissioner of Health. The Task Force has produced reports on issues including the withholding and withdrawing of life-sustaining treatment, surrogate decision-making, assisted reproductive technologies, organ transplantation, dietary supplements, genetic testing, and the allocation of ventilators in an influenza pandemic.

This report is the culmination of the hard work of the members of the Task Force and the Task Force staff. Many individuals have played a large role in this comprehensive work. It is important to acknowledge Valerie Gutmann Koch who has served as the Senior Attorney and, more recently, as a Consultant to the Task Force. Additionally, this report would not have been possible without the efforts of Susie Han, who has acted as the Principal Policy Analyst, Interim Executive Director, and currently is the Deputy Director of the Task Force. Her steadfast commitment to the Task Force and this project has made the completion of this report possible and has enabled the Task Force to continue pursuing its mission.

The quality of the work is a testament to all the effort that was put into it by Task Force members, staff, and individuals who volunteered to assist in the report's development. We hope that this report provides researchers in New York with the guidance to conduct ethical projects and, most importantly, that it provides essential protections for individuals who do not have the capacity to consent to such research.

Sincerely,

Stuart C. Sherman, J.D., M.P.H.
Executive Director

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The New York State Task Force on Life & the Law

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I. INTRODUCTION

Human subjects research plays an essential role in advancing biomedical and behavioral science and strengthening our ability to prevent and treat human diseases and medical conditions. The optimal condition for research involving human subjects is for the participant to provide first-person informed consent. To learn about and seek cures for the broad range of diseases that impair cognition, however, research requires the participation of individuals who cannot themselves provide informed consent. Due to legitimate concerns about vulnerability and exploitation, this population has been specially protected in the realm of biomedical research, sometimes to the point of exclusion. Concerns about how to conduct research involving individuals unable to give first-person informed consent are valid and important. Yet justice requires us to devise guidance and procedures that will allow these individuals to benefit from scientific advances while ensuring that their interests are protected.

Although research involving adults lacking consent capacity is permitted in New York State, until recently it was limited because of uncertainty about who could provide surrogate consent to participation. In 2010, a new State law, the Family Health Care Decisions Act, changed the legal landscape by permitting surrogate consent to health care and potentially opened up the field of research requiring surrogate consent. However, there remain few rules and little guidance at both the federal and State level to ensure that there is consistently ethical conduct of research involving adults lacking consent capacity.

In this report, the New York State Task Force on Life and the Law (the Task Force)¹ presents and assesses legal and ethical considerations, identifies policy options, and makes recommendations regarding the conduct of research in New York involving adults who lack consent capacity. An underlying goal of this work is to ensure that research protocols are available to all individuals, including this population, so that they may also experience the benefits of research and share its risks and burdens as their non-cognitively impaired peers, while also ensuring the appropriate level of protections. Thus, this report will provide guidance and best practices that will assist institutions, researchers, institutional review boards, and surrogate decision-makers in the ethical conduct and responsibilities of research involving the cognitively impaired.

II. BACKGROUND

A. History of Human Subjects Research

The history of human subjects research in the United States has at times been troubling. In one of the most notorious studies, United States Public Health Service researchers investigating the progression of syphilis failed to treat participants, or inform them of available

¹ Established by Executive Order in 1985, the Task Force is composed of approximately 23 Governor-appointed leaders in the fields of religion, philosophy, law, medicine, nursing, and bioethics. The Task Force develops public policy on issues arising at the interface of medicine, law, and ethics, and has issued influential reports on cutting-edge bioethics issues. See Appendix A for the Task Force members and http://www.health.ny.gov/regulations/task_force/ for the list of past and current Task Force projects.

treatments, even once penicillin became widely available for treatment. From 1932 to 1972, nearly 400 impoverished African Americans were included in the study, many of whom died of syphilis or syphilis-related conditions. The experiment, which became known as the Tuskegee Syphilis Study, persists as an infamous example of non-consensual, harmful research.²

New York State has not been immune to human subjects research scandals. The *New England Journal of Medicine*'s publication of Dr. Henry Beecher's 1966 review of unethical research studies references a number of examples that occurred within New York institutions.³ In one example, the Willowbrook State School, a New York residential institution for developmentally disabled persons, asked parents to give "consent" for the deliberate infection of their children with hepatitis, although the risks to the children were not disclosed.⁴ Some of the children were then treated with immunoglobulins in an attempt to diminish the effect of the disease, while others served as control subjects. In some cases, children waiting for admission to the institution gained entry when parents agreed to enroll their child in the study since the only available rooms were in the experimental ward. In another instance cited in the article, researchers from Memorial Sloan-Kettering injected cancer cells into twenty-two institutionalized elderly patients at the Jewish Chronic Disease Hospital. Patients were not informed that they were exposed to cancer but were told only that they would receive "some cells."⁵

Dr. Beecher's article drew attention to two specific features of unethical research: lack of informed consent and the risk of significant harm, including fatalities. The aforementioned studies are particularly disturbing because many of the research participants were particularly vulnerable – developmentally impaired, economically disadvantaged, or elderly – and were often chosen as participants precisely *because* they were vulnerable and unable to decline. Beecher's article, and its subsequent press coverage, elicited enormous public reaction, dovetailing with other evidence emerging in that era of the inadequate regulation of human subjects research. Federal and state legislators responded with a range of efforts to create legal barriers to unethical research in an attempt to prevent the recurrence of similar outrages.

B. Legal Oversight of Human Subjects Research Involving Participants Lacking Consent Capacity

1. Federal Law

In response to the revelation of research scandals, Congress passed the National Research Act in 1974, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission). One of the responsibilities of the National Commission was to identify the ethical principles that should be the foundation of human subjects research and to develop guidelines to assure that such research is conducted in

² Tuskegee Syphilis Study Legacy Committee, *Final Report of the Tuskegee Syphilis Study Legacy Committee* – May 20, 1996, http://www.hsl.virginia.edu/historical/medical_history/bad_blood/report.cfm.

³ Henry K. Beecher, *Ethics and Clinical Research*, 274 N. ENGL. J. MED. 367, 371 (1966).

⁴ Carl H. Coleman et al., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* at 39 (LexisNexis 2005).

⁵ *Id.*

accordance with those principles. The National Commission's 1979 report, also known as the Belmont report, enunciated values by which research involving human subjects should be conducted.⁶

In turn, the Belmont Report became the basis for much of the federal Department of Health and Human Services (HHS) regulations, including the so-called Common Rule, that now govern a majority of human subjects research in the country.⁷ The Common Rule applies to research that uses federal funding, is conducted by the federal government, or is overseen by a federal agency. Among its other elements, it lays out detailed requirements regarding institutions' responsibilities to assess research protocols and for obtaining and documenting informed consent – including disclosure of potential risks and benefits – to minimize the possibility of coercion or undue influence on research participants.⁸ It requires that an institutional review board (IRB)⁹ approve all studies involving human subjects to assure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research.¹⁰

Where participants are “likely to be vulnerable to coercion or undue influence” – including children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons – IRBs must require that researchers utilize “additional

⁶ The Nat'l Comm'n for the Protection of Human Subjects of Biomedical and Behavioral Research, THE BELMONT REPORT (1979), available at <http://www.hhs.gov/ohrp/policy/belmont.html>. [hereinafter THE BELMONT REPORT].

⁷ The Common Rule is Subpart A of 45 C.F.R. 46. The Common Rule (formally “The Federal Policy for the Protection of Human Subjects”) has been adopted by eighteen federal government agencies to promote uniformity in the conduct of human subjects research. See generally 45 C.F.R. Part 46. Such research is primarily overseen by the Office of Human Research Protections (OHRP), an office within HHS, which ensures regulatory compliance and provides guidance for the conduct of such research. See generally US Department of Health and Human Services, OHRP Fact Sheet – December, 2009, <http://www.hhs.gov/ohrp/about/facts/index.html>. The Food and Drug Administration (FDA) has adopted similar, but not identical, regulations. See generally 21 C.F.R. Part 56. Only subpart A of 45 C.F.R. 46, the Basic HHS Policy for Protection of Human Research Subjects, is identified as the Common Rule. The Common Rule is also consistent with the Declaration of Helsinki (recommendations by the World Medical Association (WMA) for research involving human subjects). The Declaration of Helsinki was originally adopted by the WMA in 1964, and the most recent amendments were adopted in October 2013. The newest new version acknowledges the need to include previously excluded populations in research, but “prohibits individuals who cannot consent from participating in research that does not address the condition that caused their incapacity, even when the research offers participants the potential for important medical benefit and there are no – or few – potential participants who can consent.” See Joseph Millum, David Wendler, & Ezekiel J. Emanuel, *The 50th Anniversary of the Declaration of Helsinki: Progress but Many Remaining Challenges*, JAMA (Oct. 19, 2013), available at <http://jama.jamanetwork.com/article.aspx?articleid=1760320>.

⁸ 45 C.F.R. §§ 46.116-17.

⁹ An Institutional Review Board (IRB) is a committee established to review and approve research protocols that involve human subjects. IRBs are used to protect the rights and welfare of research participants.

¹⁰ For the first time in two decades, HHS is contemplating major changes to the Common Rule. See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (July 26, 2011); Ezekiel J. Emanuel & Jerry Menikoff, *Reforming the Regulations Governing Research with Human Subjects*, 365 N. ENGL. J. MED. 1145 (2011). The Advance Notice of Proposed Rule Making (ANPRM) suggests, among other things, the modification and streamlining of informed consent forms, implementation of a risk-based review process, standardization of data security measures, expansion of the jurisdiction of the Common Rule to govern all studies conducted in institutions that receive federal funding, and centralized IRB review. However, the ANPRM only proposes changes to the Common Rule itself (Subpart A of 45 C.F.R. 46), without specifically addressing the protection of vulnerable populations or adding a subpart with explicit protections for individuals with diminished decision-making capacity.

safeguards” to protect participants’ rights and welfare.¹¹ Federal rules enunciate extra requirements and safeguards for certain specific vulnerable populations: (1) pregnant women, fetuses, neonates; (2) prisoners; and (3) children.¹² However, the HHS regulations do not have a similar subpart or a detailed description of necessary additional protections for governing research involving individuals who are “mentally disabled.”

In 2006, the Office of Human Research Protections (OHRP), an office within HHS, which ensures regulatory compliance and provides guidance for the conduct of such research, convened a subcommittee of its Secretary’s Advisory Committee on Human Research Protections (SACHRP) to address the lack of guidance addressing research with the cognitively impaired. Known as the Subcommittee on the Inclusion of Individuals with Impaired Decision-Making in Research (SIIDR), the subcommittee’s charge was to “develop recommendations for consideration by SACHRP about whether guidance and/or additional regulations are needed for research involving individuals with impaired decision-making capacity.”¹³ SIIDR developed ten recommendations for regulatory and oversight policy that were approved by SACHRP and forwarded to the Secretary of HHS for her consideration in 2009, but no further action has been taken.¹⁴

¹¹ 45 C.F.R. § 46.111(b). “Additional safeguards” that the Office of Human Research Protections (OHRP) has deemed acceptable may be found in OHRP Compliance Determination Letters. As the regulations do not provide examples of additional safeguards, and OHRP does not have a consolidated list of them, it is instructive to review OHRP determination letters for instances where they have addressed the issue in the course of a compliance investigation. *See, e.g.*, Letter from Dr. Kristina C. Borrer, Compliance Oversight Coordinator at OHRP, to Dr. Ming T. Tsuang, Head, Harvard Dept. of Psychiatry, Massachusetts Mental Health Center & Dr. Lester Grinspoon, Executive Director, Massachusetts Mental Health Research Corporation (July 24, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/jul02g.pdf; Letter from Dr. Michael A. Carome, Director of Division of Compliance Oversight at OHRP, to Mr. John M. Allen, Assistant Vice President for Scientific Affairs, Health Science Center at SUNY Downstate Medical Center & Mr. John O’Hara, Research Foundation Campus Operations, Health Science Center at SUNY/Downstate Medical Center (April 17, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/apr02r.pdf (finding corrective actions taken by the IRB including the use of independent consent monitors, subject advocates, special education techniques, assessment of participants’ comprehension, and consent waiting periods sufficient additional safeguards for research with potentially vulnerable populations).

¹² Subparts B, C, and D enunciate protection of pregnant women, fetuses, and neonates; prisoners; and children, respectively. *See generally* 45 C.F.R. §§ 46.201-409.

¹³ *See* OHRP, *Secretary’s Advisory Committee on Human Research Protections (SACHRP) Subcommittees*, <http://www.hhs.gov/ohrp/sachrp/subcommittees/index.html> (last visited April 16, 2013).

¹⁴ *See* Letter from SACHRP, Advisory Committee to the OHRP, to the Honorable Kathleen Sebelius, Secretary of Health and Human Services (July 15, 2009), <http://www.hhs.gov/ohrp/sachrp/20090715lettertohhssecretary.html>. The recommendations include detailed discussions and request for guidance on matters such as additional safeguards pursuant to 45 C.F.R. § 46.111, selection and responsibilities of legally authorized representatives (LARs), and a request for further clarification of the OHRP interpretation of the federal regulations deference to “applicable law” as used to define LARs. The final two recommendations call for new regulations, including a new Subpart to the Common Rule that would include a hierarchy of individuals qualified to serve as a research LAR in the absence of applicable state law, to promote uniformity among states with regard to their regulation of surrogate consent to research. *See also* SACHRP, RECOMMENDATIONS FROM THE SUBCOMMITTEE FOR THE INCLUSION OF INDIVIDUALS WITH IMPAIRED DECISION MAKING IN RESEARCH (SIIDR), <http://www.hhs.gov/ohrp/sachrp/20090715letterattach.html> (last visited April 16, 2013) [hereinafter “SIIDR RECOMMENDATIONS”].

This dearth of guidelines leads to uncertainty by IRBs regarding how to conduct studies involving these participants, which often results in either forgoing research in relevant fields or significant inconsistency in the protections of adults lacking consent capacity.¹⁵

2. New York State Law

As Congress was examining human subjects research, the New York State Legislature was also proceeding with its own legal remedy to address the conduct of human subjects research. In 1967, after hearing testimony regarding research scandals in the State, the Legislature introduced a bill to protect human participants from unethical and unnecessarily harmful research, while still permitting beneficial research to continue.¹⁶ In 1975, New York enacted Public Health Law Article 24-A. This law explicitly identified protection of participants in research as a primary goal of the law, and also recognized the benefits of allowing human subject participation in research for the advancement of medicine, while emphasizing the need for safeguards.¹⁷ It defined and addressed the necessity of voluntary informed consent and lays out the mechanisms by which a Human Research Review Committee (HRRC) reviews proposed research protocols.¹⁸

Notably, the State Legislature provided that Article 24-A only applies to research *not* covered by federal law. Specifically, the provisions of 24-A do not pertain to research “subject to, and which is in compliance with, policies and regulations promulgated by any agency of the federal government for the protection of human subjects.”¹⁹ Thus, Article 24-A applies to only a

¹⁵ For example, OHRP has found that often IRBs failed to require any additional safeguards beyond the requirement of surrogate consent. *See, e.g.*, Letter from Dr. Kristina C. Borrer, Compliance Oversight Coordinator at OHRP, to James Wagner, Interim President, Case Western University & Farah M. Walters, President and CEO, University Hospitals of Cleveland (March 26, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/mar02p.pdf, and Letter from Carol J. Weil, Compliance Oversight Coordinator at OHRP, to Dr. Neal Nathanson, Vice Provost for Research, University of Pennsylvania (April 30, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/apr02ad.pdf.

¹⁶ The bill was intended to “correct an obvious omission by bringing into law the prohibition of involuntary human experimentation. Many abuses have transpired in New York State that can be put in the category of cruel and inhuman experimentation.” Memorandum of Assemblyman Alan G. Hevesi, “Protection of humans in research,” 1975 N.Y. Legis. Ann., at 274-275.

¹⁷ N.Y. Pub. Health Law § 2440. Article 24-A states:

The use of human subjects in medical research projects has brought about many beneficial scientific advances resulting in the increased health and well-being of the human race. Safeguarding the rights and welfare of individual human subjects in the conduct of these human research projects is a matter of vital state concern. Every human being has the right to be protected against the possible conduct of medical or psychological research upon his body without his voluntary informed consent. Human research may effect dangerous and unanticipated results causing irreversible damage to the human subject. Accordingly, it shall be the policy of this state to protect its people against the unnecessary and improper risk of pain, suffering or injury resulting from human research conducted without their knowledge or consent.

¹⁸ An HRRC is the State’s equivalent of an IRB. N.Y. Pub. Health Law § 2444.

¹⁹ N.Y. Pub. Health Law § 2445. This section applies to research that is not subject to federal regulations even if the sponsoring institution submits to the HHS a “multiple project assurance,” voluntarily agreeing to comply with federal human subjects research regulations. *See T.D. v. N.Y.S. Office of Mental Health*, 228 A.D.2d 95 (First Dept. 1996); *aff’d in part* 91 N.Y.2d 860.

minority of research activity in the State, as most research conducted in New York is either federally funded or otherwise subject to federal oversight.²⁰

Article 24-A explicitly contemplates research with cognitively impaired adults. Article 24-A defines informed consent as “the legally effective knowing consent of an individual *or his legally authorized representative . . .*”²¹ Similarly, the law states that, “[i]f the human subject be otherwise legally unable to render consent, such consent shall be subscribed to in writing by *such other person as may be legally empowered to act* on behalf of the human subject.”²² Finally, Section 2444(2), as it describes the responsibilities of the HRRC, requires “the consent of the committee and the commissioner . . . with relation to the conduct of human subjects research involving minors, *incompetent persons, mentally disabled persons* and prisoners.”²³ In short, the Legislature clearly intended that research include certain vulnerable populations, subject to additional safeguards. However, similar to the Common Rule, Article 24-A does not provide detailed procedures for the ethical conduct of such research beyond these general provisions.

III. DEVELOPMENT OF HUMAN SUBJECTS RESEARCH GUIDELINES

Although legal protections were instituted to prevent exploitation of participants in research, the unintended consequence of such laws was overprotective policies for research involving certain vulnerable populations such as the cognitively impaired. In more recent years, the research community and certain patients’ rights advocates have formed an unlikely union in arguing that laws designed to protect the cognitively impaired actually disadvantage this population by barring even worthwhile research, thereby preventing discovery of cures and treatments for conditions that cause decisional incapacity.²⁴

²⁰ The reach of Article 24-A is limited not only by the fact that it excludes federally regulated research; it is further limited by employing a definition of “human research” that is narrower than the definition of “human subjects research” under federal regulations. Accordingly, purely behavioral, social science, and epidemiological research is not regulated under Article 24-A. *Compare* N.Y. Pub. Health Law § 2441(2) (defining “human research” as “any medical experiments, research, or scientific or psychological investigation . . . which involves physical or psychological intervention by the researcher upon the body of the subject and which is not required for the purposes of obtaining information for the diagnosis, prevention, or treatment of disease or the assessment of medical condition for the direct benefit of the subject. Human research shall not, however, be construed to mean the conduct of biological studies exclusively utilizing tissue or fluids after their removal or withdrawal from a human subject in the course of standard medical practice, or to include epidemiological investigations.”), *with* 45 C.F.R. § 46.102(d) (“Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.”).

²¹ N.Y. Pub. Health Law § 2441 (emphasis added).

²² N.Y. Pub. Health Law § 2442 (emphasis added).

²³ N.Y. Pub. Health Law § 2440 (emphasis added). Although the Commissioner of Health is required to review such protocols, a New York State Multiple Project Assurance (MPA) may obviate the need for full Commissioner review for certain research studies and risk levels. *See* Section X.C for a discussion on MPAs.

²⁴ Remarks at the Meeting of SACHRP (Oct. 27-28, 2008), <http://www.hhs.gov/ohrp/sachrp/mtgings/mtg10-08/minutes.html>.

At the request of various stakeholders, the New York State Department of Health (the Department of Health) asked the Task Force to embark on a project to analyze the legal and ethical implications of proceeding more broadly with research involving adults lacking consent capacity. The Task Force began in December 2007 by disseminating a survey to approximately 300 New York IRB chairs and members that requested information about their institutions' practices, if any, for conducting research involving the cognitively impaired, and their views on the regulatory landscape. Mindful that facilities might resist direct inquiry for fear of government sanctions, the survey was crafted to allow anonymous internet responses. This design permitted more candid responses, but impeded detailed statistical analysis.²⁵ More than 100 responses provided a detailed and useful qualitative account of research practices in New York, and indicated a need for guidelines to ensure consistently ethical research practices.

The survey confirmed that, in the absence of a person with legal authority to consent on behalf of a cognitively impaired individual's participation in research, institutions had two basic responses: they either (1) abstained entirely from research that required surrogate consent, or (2) engaged in such research despite the lack of clear authority. The majority of respondents reported that their institutions permitted the use of surrogate consent for research involving adults lacking consent capacity for at least certain forms of research, but there was little consistency in how IRBs reviewed these research protocols. Institutions used a broad range of standards for selecting and informing surrogates, evaluating potential participant's decision-making capacity, and protecting and safeguarding participants' rights. Furthermore, numerous respondents described several problems in the assessment of capacity: they were uncertain when to screen for or evaluate capacity, what measures to use to evaluate capacity, and who should perform such evaluations. In addition, the composition of IRB membership and use of outside consultants with expertise in evaluating decision-making capacity varied widely, which affected the thoroughness of the review process.

Some participant institutions indicated that the lack of standardized guidelines prevented access to treatment under research for individuals who lack consent capacity. Other respondents noted that uncertainty had stymied appropriate research at their institutions and expressed concern that research continued at other settings with less oversight. Many participants requested that the State provide additional guidance for the conduct of research involving adults lacking consent capacity.

Since the survey was conducted, the Task Force has examined the ethical and legal issues associated with research involving adults lacking consent capacity. It reviewed medical and policy literature on human subjects research, informed consent, surrogate consent, capacity assessment, risk-benefit analysis, research protections, and related topics. It conducted extensive legal research of federal and state regulatory standards, including New York's, and case studies pertaining to human subjects research involving the cognitively impaired. Several experts from research institutions, governmental entities, and patient advocacy organizations spoke at Task Force meetings. Previously released reports on human subjects research by the Department of

²⁵ The Task Force used a Freedom of Information Act request to obtain e-mail addresses of all IRBs in New York State from OHRP. Most of New York's IRBs have more than one such contact address on file with OHRP. The anonymous responses made it impossible to know if an institution provided one response, multiple responses, or no response at all.

Health and the public comments to these efforts²⁶ were analyzed by the Task Force, and stakeholders and other interested parties provided additional perspectives and input on this project.

Although the research scandals referred to above occurred decades ago, much of the public continues to have a strong mistrust of human subjects research.²⁷ Proponents of research

²⁶ Among other efforts, the New York State Department of Health commissioned an advisory work group to address the concept of surrogate consent to research, which released a draft report for public comment in 1998. See DEPARTMENT OF HEALTH ADVISORY WORK GROUP ON HUMAN SUBJECT RESEARCH INVOLVING PROTECTED CLASSES, RECOMMENDATIONS ON THE OVERSIGHT OF HUMAN SUBJECT RESEARCH INVOLVING PROTECTED CLASSES (1998), at 16, <http://www.nysl.nysed.gov/scandoclinks/ocm49377072.htm> (last visited January 8, 2013) [hereinafter 1998 NEW YORK STATE WORK GROUP REPORT]; see also AD HOC WORKGROUP CONVENED BY THE NEW YORK ACADEMY OF MEDICINE, CONSENT FOR RESEARCH WITH DECISIONALLY INCAPACITATED ADULTS (2004) (on file with the Task Force). Additionally, the New York State Office of Mental Health promulgated regulations in 1990 governing research with adults lacking consent capacity, but they were struck down on the basis that only the Commissioner of Health was provided with the authority to promulgate regulations under Article 24-A. *T.D. v. N.Y. State Office of Mental Health*, 165 Misc.2d 62, 73 (N.Y. Sup. Ct. 1995), *aff'd* 228 A.D.2d 95 (N.Y. App. Div. 1996), *aff'd in part, rev'd in part*, 91 N.Y.2d 860 (1997). *But see* 14 N.Y. Comp. Codes R. & Regs. tit. 14, § 27.10 (effective 1975). In *T.D.*, the court addressed whether the Office of Mental Health had the authority to promulgate regulations regarding human subjects research, and in finding that it did not, the court specifically held that this power lies with the Commissioner of Health. 165 Misc.2d at 73.

²⁷ Unethical research continues to be covered by the media as past misconduct comes to light, with recurring themes, including lack of respect, exploitation of individuals of certain racial/ethnic/class/educational backgrounds, and compensation and privacy issues of the participants. Recent examples of research scandals discovered within the last few years include the unauthorized taking and use of the HeLa cell lines from Henrietta Lacks, improper use of biological samples from the Havasupai Native Americans outside of the informed consent protocol, and the deliberate infection with a disease to test a drug (Guatemala venereal disease study). The HeLa cancer cell lines were taken from Henrietta Lacks without her consent in 1951 and commercialized for ground-breaking scientific advances. Ms. Lacks soon after died from cervical cancer and her family was never informed that the cells existed for more than 20 years after her death. They did not receive any compensation for the millions in profits the cells have generated. The research scandal affirmed the belief in the community that a black woman's body is often exploited by white scientists. Jacqueline H. Wolfe, *The Immortal Life of Henrietta Lacks*, 66 J. HIST. MED. ALLIED SCI. 139, 139-140 (2011) (book review). In another very public case, the Havasupai Native Americans of Arizona had an extremely high incidence of Type 2 diabetes and Arizona State University collected blood samples from members in the early 1990s to examine if there was a genetic marker for the disease. The tribe members agreed to submit blood samples solely for research involving Type 2 diabetes. They were not informed that their blood samples would be used for research into schizophrenia, inbreeding, and ancient population migration. In a lawsuit, the Havasupai claimed research beyond diabetes research was an invasion of privacy and a source of shame, and as a result, many members feared seeking medical attention. In April 2010, the University's Board of Regents settled, agreeing to pay \$700,000 to members of the tribe, return the blood samples obtained between 1990 and 1994, and provide other forms of assistance. Michelle M. Mello & Leslie E. Wolfe, *The Havasupai Indian Tribe Case – Lessons for Research Involving Stored Biologic Samples*, 363 N. ENGL. J. MED. 204, 204 (2010); Amy Harmon, *Tribe Wins Fight to Limit Research of its DNA*, N.Y. TIMES, Apr. 22, 2010, at A1, http://www.nytimes.com/2010/04/22/us/22dna.html?pagewanted=all&_r=0. Moreover, in studies conducted in the 1940s that recently came to light, approximately 700 Guatemalans – prison inmates, mental patients and soldiers – were deliberately infected with venereal diseases to test the effectiveness of penicillin. Among other means of infecting the “participants,” American tax dollars, through the National Institutes of Health, paid for syphilis-infected prostitutes to sleep with the men. When the prostitutes did not succeed in infecting the men, some individuals had the bacteria poured onto scrapes made on their penises, faces or arms, or injected by spinal puncture. Antibiotics were given to those who contracted the disease, but it was not clear from the research documents if all the participants were cured. Nellie Bristol, *US Reviews Human Trial Participant Protections*, 376 THE LANCET 1975, 1975 (2010). As a result of the Guatemala scandal, President Obama asked the Presidential Commission for the Study of Bioethical Issues to review federal guidelines for protecting humans during medical testing.

often state that while concerns surrounding research are valid and should be addressed, ethical research is possible and especially needed for individuals who suffer from cognitive impairment. The development of a policy that provides guidance to IRBs and researchers would help to ensure that only ethical and valuable scientific research is conducted while simultaneously protecting the rights and welfare of this population.

The Task Force is releasing this report to analyze the various legal and ethical considerations and policy options regarding research involving adults lacking consent capacity. Historically, along with children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, individuals lacking consent capacity have been referred to as members of a “vulnerable” population.²⁸ “Vulnerable” status may be assigned due to an individual or group’s condition or situation. For example, many of these individuals are at a heightened risk of coercion or undue influence because they may be unable to make autonomous decisions due to their inability to weigh the risks involved with a protocol. There may be an increased risk of harm to themselves and to others if they should participate in a research protocol. The remainder of this document will provide illustrative guidance and best practices that will assist institutions, IRBs, researchers, and surrogate decision-makers in the ethical conduct of research involving the cognitively impaired. The Task Force hopes such guidance will promote a consistently ethical approach by institutions to the protection of this vulnerable population in New York State.

IV. VALUES UNDERLYING HUMAN SUBJECTS RESEARCH

A. Ethical Values

According to the 1979 Belmont Report, research should adhere to the following three ethical values: respect for persons, beneficence, and justice. The first of these values, respect for persons, addresses at least two ethical concerns: (1) that individuals should be respected as autonomous agents, and (2) that individuals with impaired consent capacity need protection against abuse.²⁹ An autonomous individual can consider and act upon personal goals and to respect such an individual is to accept his/her opinions and decisions – so long as these actions do not harm others. The value of respect for persons encourages potential participants to be involved in the decision-making process, assuring them that they have an essential role in the research and that their opinions and decisions are valued. It also reminds researchers that all participants should be treated with dignity and respect and that they are not merely objects to be used for the purpose of research. In addition, respect for persons may require particular attention

Memorandum from Barack Obama, President of the United States of America, to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (Nov. 24, 2010), <http://www.whitehouse.gov/the-press-office/2010/11/24/presidential-memorandum-review-human-subjects-protection>. The Commission released its report, *Ethically Impossible*, in September 2011. Presidential Comm’n for the Study of Bioethical Issues, “*Ethically Impossible*” *STD Research in Guatemala from 1946 to 1948* (Sept. 2011), http://bioethics.gov/cms/sites/default/files/Ethically_Impossible%20%28with%20linked%20historical%20documents%29.pdf.

²⁸ See, e.g., 45 C.F.R. § 46.111(b) (requiring “additional safeguards” where participants are “likely to be vulnerable to coercion or undue influence”).

²⁹ THE BELMONT REPORT, *supra* note 6, at 5-6.

to protecting certain populations, such as adults who have limited consent capacity, although the level of protection may depend on the degree of cognitive impairment.

The second value, beneficence, is best understood as two complementary values: (1) do no harm, and (2) to the extent avoiding harm is not possible, maximize the possible benefits and minimize the possible harms.³⁰ It may be difficult, however, to determine when the conduct of human subjects research is, or is not, justified to pursue possible benefits despite the risks of such research. While beneficence requires that cognitively impaired adults should be protected from unreasonable risk, it must also require the consideration of the potential loss of benefits that would have otherwise been received from conducting the research, both to the participants and to other similarly impaired individuals. For example, should research with a significant risk level and no assurance of benefit to participants – but which has the potential to benefit similarly situated individuals in the future – always be avoided? This question often turns in part on whether the research protocol is intended to provide any benefit to any of the participants, or whether the goal is only to elicit new knowledge. The requirement that all populations be protected from unreasonable risk and harm and that reasonable efforts be made to safeguard their well-being may necessitate special safeguards in the case of vulnerable populations whose ability to protect themselves may be compromised.

The third key value is justice – “fairness in distribution” – in terms of who should bear the risks and realize the benefits associated with research.³¹ In accordance with this value, those who bear the research risks should also receive appropriate benefit, and those who will most likely benefit from the research should undertake a fair proportion of the risks. In other words, research should be an option available to all individuals, including adults lacking consent capacity, so that they may also experience the benefits of research and share its risks and burdens as do their non-cognitively impaired peers.

Thus, justice also requires access to research opportunities. There is a delicate balance that should be achieved to provide research options to which a person is entitled without an imposition of a disproportionate burden to that individual. To deny access to research for a particular group has far-reaching consequences. In the past, hesitation in conducting research involving cognitively impaired individuals has limited research that could benefit this population and was an impediment to the advance of knowledge of the diseases or medical conditions that cause cognitive impairment. Nevertheless, it may be prudent to require specific conditions and safeguards, and a higher threshold which research studies involving certain vulnerable populations must meet, to prevent exploitation of adults lacking consent capacity.

In addition to the values from the Belmont Report, the Task Force also seeks to promote the principle of transparency as a requirement for the ethical conduct of research involving human subjects. Transparency in setting policy for, and conducting, human subjects research is essential to public trust in the research enterprise. Particularly because of persistent public misgivings about the harms that may arise in research involving cognitively impaired individuals, it is imperative that researchers and IRBs meet – and be seen to meet – the highest ethical standards when conducting and reviewing research protocols. Studies involving

³⁰ *Id.*

³¹ *Id.*

vulnerable populations should promote transparency in all aspects of the research, including study design and the IRB's initial and continuing review of the protocol. Researchers and IRBs should document deliberations and conclusions to ensure accountability. Accurate disclosure of the potential risks and benefits, ongoing research findings, and other relevant information should be provided in a clear and accessible fashion. Making the process of research review and approval more transparent will encourage public confidence and willingness to participate in research requiring human subjects.

B. Participant Selection/Justification

Scandals such as those that occurred at Willowbrook and the Jewish Chronic Disease Hospital were particularly objectionable not only because researchers enrolled participants without their informed consent, but also because the participants were selected precisely *because* they were vulnerable and unable to decline.

To prevent similar ethical lapses, scholars have proposed the use of a “necessity principle” (i.e., allowing research involving vulnerable populations only where the desired information cannot be obtained by enrolling non-vulnerable groups).³² There are two variations of this principle. The stricter version imposes a “subjects’ condition” requirement, such that a researcher may only use a specific impaired population when the research study seeks to ameliorate the cause of the group’s disability.³³ The more permissive version of the principle allows participation of those lacking consent capacity for protocols that do not target the specific condition causing the cognitive impairment, but examines a condition that uniquely affects this population.³⁴ Defenders of the subjects’ condition requirement posit that it provides the greatest level of assurance that participants are not exploited by being selected merely for their compliant behavior, while proponents of the permissive viewpoint argue that the subjects’ condition requirement is overly restrictive in that it prohibits otherwise ethical research that requires participation of impaired individuals.³⁵ For example, under the stricter version of the subjects’ condition requirement, a protocol studying the treatment of bedsores that involved individuals with Alzheimer’s disease would be barred.

The Task Force recommends that researchers and IRBs must ensure that there is justification for involving participants who lack consent capacity in research protocols, and in general, that the least burdened populations should be used as research participants wherever possible. Availability, compromised position, or ease of recruitment are insufficient reasons to

³² Henry J. Silverman et al., *Protecting Subjects with Decisional Impairment in Research*, 169 AM. J. RESPIRATORY & CRIT. CARE MED. 10, 12 (2004).

³³ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 28; OFFICE OF THE MARYLAND ATTORNEY GENERAL, FINAL REPORT OF THE MARYLAND ATTORNEY GENERAL’S RESEARCH WORKING GROUP (1998), at A-16-17 [hereinafter MARYLAND ATTORNEY GENERAL REPORT]; Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 12.

³⁴ Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 12.

³⁵ Some commissions have recommended using the necessity principle only for non-therapeutic studies, *see, e.g.*, 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 16, while others advocate it regardless of the study’s potential benefit, *see, e.g.*, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, TRI-COUNCIL WORKING GROUP ON ETHICS, CODE OF CONDUCT FOR RESEARCH INVOLVING HUMANS (1997), at VI-1.

justify the inclusion of a specific vulnerable group in research. The inclusion of such individuals may be appropriate in research that offers potential benefits to participants when standard clinical approaches are ineffective, unproven, or unsatisfactory, or when research is reviewing a new, improved standard of care that may be more effective for conditions that uniquely affect that specific population. Furthermore, IRBs should pay particular attention to the rationale behind enrolling vulnerable patients for research protocols that do not explicitly study medical conditions that impair consent capacity.

In addition, the Task Force recommends that the institutional setting for research must be scrutinized when choosing the least burdened population. If researchers propose to utilize nursing home residents or institutionalized patients, they should demonstrate why that venue is necessary,³⁶ because research involving these groups may be seen as increasing the risks and potential harms for an already burdened population. Many of these residents have an additional layer of vulnerability due to their heavy reliance for care on staff members, some of whom may be part of the research study or involved in recruitment, and the residents may therefore be subject to real or perceived coercion by staff to participate.

Where possible, particularly for high risk or no-direct-benefit research, IRBs should require research protocols to include evidence of safety and efficacy data from studies conducted in a non-impaired group prior to inclusion of cognitively impaired individuals. However, in certain circumstances, the potential benefit is unique to the cognitively impaired population, or the characteristics of the non-impaired participants may differ so greatly from the impaired population that such evidence may not be available.

V. IRB REVIEW AND CONFLICTS OF INTEREST

A. Human Research Review Committees and Institutional Review Boards

Under both federal and state law, IRBs must review, approve, and oversee research protocols.³⁷ IRBs, and the State equivalent, “human research review committees” (HRRCs) (which will be referred to collectively as IRBs hereinafter), provide direct review and approval of research and are thus a primary institutional safeguard in place to protect vulnerable populations from unethical research. These review committees can help encourage public confidence in research and in oversight activities by fostering and nurturing public trust that research is executed in an ethically responsible manner. IRBs provide guidance to researchers about the conduct of appropriate research, particularly for research that has a lesser likelihood of direct benefit or higher risk.

When IRBs review research protocols that involve adults lacking consent capacity, they should consider carefully the extent to which the research aims to improve the understanding, diagnosis, prevention, or treatment of the disorders or conditions that are the cause of the incapacity, or that commonly or uniquely affect individuals who lack capacity. However,

³⁶ Possible justifications may include that these institutionalized settings provide additional oversight and monitoring of participants and the research, and that these settings contribute to the overall standardization and integrity of the data.

³⁷ 45 C.F.R. §§ 46.107-111; N.Y. Pub. Health Law § 2444.

striking a balance between protection and access is difficult, complicating IRB review of research protocols. Although IRBs should prohibit inclusion of any populations in research involving undue or unjustified risk, they should be especially mindful of justice issues as well. Overprotection may result in prohibiting access to research of particular value to the impaired population and studies which exclude certain patients may significantly limit the value of the study as a whole.³⁸

Both federal and New York State laws have specific IRB membership requirements.³⁹ However, the Task Force recommends that IRBs should consider bringing in additional outside consultants, including various professionals, experts, and patient representatives, to offer guidance on research protocols involving adults lacking consent capacity. Inclusion of these additional perspectives can deepen the level of analysis and provide complementary insight to an IRB that is not accustomed to reviewing such research protocols, leading to protocols that are better designed, implemented, and more responsive to the concerns and needs of the affected population. The experiences and expertise of these additional members place IRBs in a good position to identify and evaluate potential problems posed by the protocol and will strengthen the ability of an IRB to effectively review research. Examples of those that might be invited include:

- Patients affected by relevant diseases that impair cognition, former patients, patient advocates, family members, or others who can represent the view and perspectives of the research participants;
- Professionals with appropriate background, knowledge, and experience in working with individuals with impaired consent capacity;
- Individuals at facilities who can provide information relevant to the circumstances and context in which participants will be recruited;
- Specialists in the assessment of capacity and in application of legal and regulatory requirements for consent to research by a surrogate decision-maker; and
- Experts in the scientific and ethical issues relevant to studies involving vulnerable populations.⁴⁰

³⁸ See Matthew L. Flaherty et al., *How Important is Surrogate Consent for Stroke Research?* 71 NEUROLOGY 1566, 1569 (2008). This study required participants to receive a stroke treatment (recombinant tissue plasminogen activator, or rt-PA) within three hours of ischemic stroke. The majority of the study's participants were enrolled through surrogate consent, and obstacles to this form of consent would have delayed or halted a stroke trial altogether, thus preventing access to rt-PA for 10,800 to 12,600 stroke patients annually.

³⁹ In New York, HRRCs must be composed of at least five individuals, approved by the Commissioner of Health, who have such varied backgrounds to assure the competent, complete, and professional review of human subjects research activities conducted by the institution or agency. In addition, HRRC members should not be involved in either the initial or continuing review of research in which they have a conflicting interest. No committee should be comprised entirely of persons who are associated with the institution or of a single professional group. N.Y. Pub. Health Law § 2444(1). See also 45 C.F.R. § 46.107 (requiring the inclusion of one or more individuals who are knowledgeable about and experienced in working with members of the vulnerable population participating in the research).

⁴⁰ NATIONAL INSTITUTES OF HEALTH, TRANS-NIH BIOETHICS COMMITTEE WORKING GROUP, RESEARCH INVOLVING INDIVIDUALS WITH QUESTIONABLE CAPACITY TO CONSENT: NIH POINTS TO CONSIDER (2009), at 7, <http://grants1.nih.gov/grants/policy/questionablecapacity.htm> [hereinafter TRANS-NIH REPORT].

Although generally IRBs may seek assistance on topics that require expertise beyond or in addition to what is currently available on the committee, these non-members do not vote on the research protocol.

B. Conflicts of Interest

As a general matter, every research institution should ensure that conflicts of interest⁴¹ do not interfere with the welfare of the research participants, compromise the integrity of the research study, or give the appearance of impropriety. IRBs themselves should also be cautious not to underestimate or deny conflicts of interest which may be present⁴² and may choose to be more vigilant when evaluating protocols involving adults lacking consent capacity. Repeated exposure to certain conflicts of interest may lead IRBs to misjudge the potential of a conflict of interest to confound a study's validity.

Openness and honesty with full disclosure of any conflicts of interest by researchers, institutions, and other members of the research team strengthen the public's trust in the research enterprise and improve the process of informed consent. As research studies become more complicated and interaction between researchers, their institutions, and commercial ventures grows, careful attention should be given to conflicts of interest policies. For example, some financial relationships increase the likelihood that scientific advances will result in monetary gain for the researchers and affiliated institutions. Concerns also arise when non-financial factors, such as publication of the research or tenure considerations, may compromise – or give the appearance of compromising – the research design, conduct, or professional judgment of the parties involved, or threaten the welfare of participants. There is the possibility that investigators may share patient information with fellow researchers when motivated by political or personal commitments, or seeking career advancement.⁴³

To this end, the Task Force recommends that institutions and IRBs rigorously scrutinize a research protocol – especially those involving adults without consent capacity – for any potential or actual conflict presented by an institution, a researcher, and any other individual who is responsible for the design, operation, or reporting of the study. If it is determined that an unacceptable conflict of interest exists, the interested party may not proceed with the research study unless the conflict is removed. If necessary, the IRB should not approve a research study.

⁴¹ An institution's conflict of interest policy should: (1) specify what individuals and entities would be affected by the policy, including notification and disclosure procedures, (2) determine what types of interests may pose conflicts, including defining what may constitute a significant financial, personal, or professional interests, which may include direct or indirect monetary interests in the research (i.e., equity interests), compensation or incentives contingent upon the results of the research, intellectual property rights (i.e., patents or royalties), reimbursement for professional services (i.e., for speaking or consulting engagements, or by gifts, honoraria, or payment for travel, lodging or registration expenses at conferences), or professional advancement (i.e., publications or additional grant money), (3) develop a procedure to manage disclosed conflicts of interest to ensure that the welfare of the research participants and the integrity of the study are not compromised, (4) delineate which conflicts of interest would require disqualification from review, conduct, or participation in the proposed research and which conflicts require only disclosure to the IRB, the potential participant, or surrogate decision-maker; and (5) establish review and enforcement mechanisms and provide for appropriate sanctions.

⁴² Robert Klitzman, "*Members of the Same Club*": Challenges and Decisions Faced by US IRBs in Identifying and Managing Conflicts of Interest, 6 PLoS ONE 1, 6 (2011).

⁴³ *Id.*

VI. BENEFITS AND RISKS

Whether to include individuals who lack consent capacity in human subjects research, and how to protect them, depends on both the benefit and risk involved.

A. Benefits

A direct benefit to a research participant consists of something gained as a result of participating in research. It may be a diagnostic, prophylactic, or therapeutic benefit; reduction of undesirable or dangerous side effects of other clinical procedures; or improvement in the social conditions of the participant. A direct benefit is not considered to include a participant's feeling of altruism or general satisfaction, or financial remuneration or other rewards, such as more intensive monitoring, as a result of participating in the research. While altruism may be a reason for individuals to participate in research to assist others similarly situated, the participants themselves do not receive an immediate positive benefit to their health or well-being. In addition, monetary incentives are not the result of the research procedure or intervention itself and therefore are not a direct benefit for these purposes. The Task Force recommends that IRBs should examine protocols to ensure that the use of financial compensation is not an undue inducement to participate in the study.

Research protocols can be classified as either a *prospect-of-direct-benefit* or *no-direct-benefit* study, based on the likelihood that the research will result in direct benefits that improve the health or well-being of a participant by procedures or interventions that are outside of standard health care treatment. Prospect-of-direct-benefit research has a reasonable probability of providing the proposed benefit. This type of benefit may occur, for instance, in late-phase clinical trials of new drugs. However, although research may offer the prospect for a direct benefit, no particular participant is assured the benefit, and, in some trials, not all participants may even have the chance to receive the benefit. For example, a clinical drug trial may offer the potential of a direct benefit (i.e., alleviation of symptoms), but some participants may not experience this benefit if they receive a placebo or the drug is not effective for them. The size of a trial often affects the measure of benefit for each subject, as well as how those conducting the trial can present the benefits.⁴⁴

However, in research, the use of the term "benefit" may be a misnomer, even when qualified to clarify the distinction between *actual* benefit and the *prospect* of benefit. It could be argued that medical interventions or procedures can only offer all patients a benefit in the treatment setting. As described in the example above, often the prospect of a benefit depends on in which arm of a research protocol the patient is placed. Furthermore, researchers may inflate the possible benefits of a research protocol in an effort to convince an IRB to approve the research or to enroll participants.

⁴⁴ Large trials may spread benefits out over a large population, which means that the therapeutic effects can be fairly small while still justifying the research. Conversely, smaller studies are often required to show evidence of more substantial benefits to justify the study. Joseph J. Fins, *Surgical Innovation and Ethical Dilemmas: Precautions and Proximity*, 75 CLEVELAND CLIN. J. MED. S7, S8-S9 (2008).

No-direct-benefit studies have a negligible or nonexistent probability of offering a benefit to participants. These studies include early-phase drug trials to identify possible side effects and basic physiological research about disease mechanisms, as well as more clearly hazardous studies involving symptom-provoking stimuli and studies in which an effective medication is withdrawn.⁴⁵

Regardless of whether a research study does or does not entail a prospect of direct benefit, IRBs should evaluate the purpose of the study and/or intent of the researcher. IRBs should only consider for approval studies that researchers demonstrate will either possibly benefit participants directly or will answer a scientific question that will further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of the studied population, thereby benefitting those similarly situated in the future. Although ideally, IRBs should look for a reasonable prospect of direct benefit to the research participant, for some innovative research protocols it would be impossible to state that such a possibility exists. In those cases, where it is unclear whether participants may benefit, the study may still be beneficial for future research and lead to the development of treatment applications for these patients later in the research process, or may benefit others with the same or similar conditions that caused the impairment being studied. In such instances, the IRB should only approve such studies when certain conditions are met.⁴⁶

The Task Force recommends that, in reviewing proposed research protocols, IRBs consider whether same or similar benefits are available outside the context of research, the intent of the researcher and purpose of the study, the likelihood that all participants will receive the benefit, and the extent or amount of the potential direct benefit. Furthermore, a prospect of benefit is non-existent only when there is zero probability of any benefit. There is also no readily identifiable upper margin of a negligible prospect of benefit, but it may be approximately one to five percent probability of benefit – close to a non-existent prospect. However, there is a wide range of probabilities of direct benefit that are more likely than non-existent or negligible prospects. These may be categorized as highly improbable (~ 5% to ~ 35% probability), somewhat improbable (~ 35% to ~ 50%), somewhat probable (~ 50% to ~ 65%), highly probable (~ 65% to ~ 95%), and virtually certain (~ 95% to ~ 99%).⁴⁷ While it is not helpful to try to quantify such degrees of probability too precisely, IRBs should recognize the wide range of probabilities encompassed by the term “prospect of direct benefit” and weigh their decisions about risk-benefit ratios accordingly.

B. Risks

One of the most complex and controversial issues in conducting research involving adults who lack consent capacity is the degree of risk to which researchers may ethically expose this population. The concept of risk has at least two dimensions: (1) the magnitude of the harm that may occur, and (2) the probability of its occurrence. Risk includes anything that may result in

⁴⁵ Carl H. Coleman, *Research with Decisionally Incapacitated Human Subjects: An Argument for a Systemic Approach to Risk-Benefit Assessment*, 83 IND. L. J. 743, 751 (2008).

⁴⁶ See Section VI.B.4 for a more in-depth discussion of circumstances when such research may be approved.

⁴⁷ These probability of direct benefit categories and assigned probability ranges are only estimates created by the Task Force to facilitate understanding of “potential direct benefit.”

emotional, psychological, physical, legal, social, or economic harm, loss of privacy, or harm to dignity. Although the harm most likely to occur may be physical or psychological, other possible types of harm should not be ignored. For example, even where physical harm will not occur, such as in a data collection study, a risk to privacy exists in the possibility of wrongful disclosure of personal information.

1. Levels of Risk

When characterizing the risk level, researchers and IRBs should note the nature and duration of the risk. A number of specific questions should be addressed, including whether exposure to the risk will result in a permanent injury; whether the injury may be remedied with treatment; and whether the impact of the risk will cease when a participant is removed from the study.

In 1977, the National Commission issued a report on research involving children, suggesting a tripartite scheme for classifying research risks.⁴⁸ These three classifications are: (1) minimal risk; (2) minor increase over minimal risk; and (3) more than a minor increase over minimal risk. This scheme was incorporated into the federal regulations for research with children,⁴⁹ and has been used in numerous expert commission reports and state regulations delineating research risk in all human subjects research.⁵⁰

As defined in the Common Rule, research presents a “minimal risk” if “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 performance of routine physical or psychological examinations or tests.”⁵¹ Procedures that are often deemed to fall into this category include blood tests, electroencephalography, questionnaires, and magnetic resonance imaging (MRI) without sedation.⁵²

⁴⁸ THE NAT’L COMM’N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING CHILDREN (1977), http://bioethics.georgetown.edu/pcbe/reports/past_commissions/Research_involving_children.pdf.

⁴⁹ The Common Rule lists three categories of acceptable types of research involving children – research that poses: (1) no greater than minimal risk; (2) more than minimal risk, where the research holds out the prospect of direct benefit so long as the risk is justified by the intended benefit and the relation of the anticipated benefit to the risk is at least as favorable as available alternative approaches; and (3) more than minimal risk, where the research does not hold out the prospect of direct benefit, so long as the risk is no more than a minor increase over minimal risk, the procedures are equivalent to everyday situations, and the research will yield important scientific knowledge about the disorder or condition being studied. 45 C.F.R. §§ 46.103, 46.109, 46.116-17, 46.405.

⁵⁰ While a few groups have utilized a bipartite scheme of minimal risk/more than minimal risk, the tripartite system is more frequently employed. Compare NAT’L BIOETHICS ADVISORY COMM’N. RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY REPORT AND RECOMMENDATIONS VOL. I. (1998), at 46 [hereinafter NBAC REPORT] (bipartite), <https://scholarworks.iupui.edu/handle/1805/21>, with 45 C.F.R. § 46 (Subpart D) (tripartite); 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 14 (tripartite); MARYLAND ATTORNEY GENERAL REPORT, *supra* note 33, at A-17 (tripartite). Notably, the NBAC REPORT’s bipartite system was widely criticized, in part because routine procedures that pose marginally greater risk than minimal risk, such as PET scans, would “be subject to restrictions on surrogate consent, which would substantially impede the ability to carry out ... important and relatively low-risk research.” See John M. Oldham et al., *Protection of Persons with Mental Disorders from Research Risk*, 56 ARCH. GEN. PSYCHIATRY 688, 690 (1999).

⁵¹ 45 C.F.R. § 46.102(i).

⁵² Oldham, *supra* note 50, at 690.

While federal regulations only define “minimal risk,” a report by the New York State Department of Health Advisory Work Group on Human Subject Research involving the Protected Classes proposed useful definitions for the other two major categories of risk.⁵³ Research presents a “minor increase over minimal risk” where:

The probability and magnitude of harm or discomfort anticipated in the research, including psychological harm and the loss of privacy or other aspects of personal dignity, are only slightly greater in and of themselves than those ordinarily encountered during the performance of routine physical or psychological examinations or tests.⁵⁴

It has been suggested that procedures that fall into the class of “minor increase over minimal risk” research include those involving positron emission tomography (PET) scans, MRIs with sedation, placement of indwelling catheters for a brief duration, and lumbar punctures with local anesthesia.⁵⁵

Research may be said to present “more than a minor increase over minimal risk” where “[s]ubjects, as a result of research participation, would be exposed to more than a remote possibility of (1) substantial or prolonged pain, discomfort or distress; or (2) clinically significant deterioration of a medical or mental condition.”⁵⁶ Examples of studies that might fall into this category include certain Phase II clinical drug trials,⁵⁷ procedures that involve general anesthesia, internal organ biopsies, bronchoscopies, and right-sided heart catheterization.⁵⁸ By its definition, research involving more than minor increase over minimal risk will involve risk that is greater than the risk involved in research involving minor increase over minimal risk. However, the difference in the probability of risk has not been quantified.⁵⁹

⁵³ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 14.

⁵⁴ *Id.*

⁵⁵ Oldham, *supra* note 50, at 690.

⁵⁶ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 14. In 2009, a workgroup of Task Force members was convened to discuss benefits, risk levels, and risk-benefit analysis. Although this workgroup acknowledged that research presents a minor increase over minimal risk where the probability and magnitude of harm are “only slightly greater” in and of themselves than those ordinarily encountered, it did not quantify the term “only slightly greater.” This imprecision might be acceptable when considering research with minor increase over minimal risk. But the imprecision is compounded, and perhaps contradicted, when considering research with more than minor increase over minimal risk.

⁵⁷ To bring a drug or treatment to market, FDA requires that clinical trials be conducted in a series of phases. In Phase I trials, researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve a larger group, to determine if the drug or treatment is effective and to further evaluate its safety. In Phase III studies, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Finally, Phase IV trials (which are often conducted after the drug or treatment has been marketed) are intended to gather information on the drug’s effect in various populations and any side effects associated with long-term use. FDA, *FAQ: ClinicalTrials.gov*, <http://www.nlm.nih.gov/services/ctphases.html> (last visited April 16, 2013).

⁵⁸ Oldham, *supra* note 50, at 690.

⁵⁹ The members of the 2009 Task Force workgroup concluded that it was difficult to compare one unquantified increase over another unquantified increase. Rather, the workgroup compared the risk of research involving more than minor increase over minimal risk to another unquantified concept: “a remote possibility” of various enumerated harms. Note that the enumerated harms are not those ordinarily encountered.

Arguably, the three primary risk categories – minimal risk, minor increase over minimal risk, and more than a minor increase over minimal risk – may be further broken down into risk subcategories. For example, IRBs that wish to consider research involving more than minor increase over minimal risk might find it useful to distinguish studies that involve *only marginally greater* than minor increase over minimal risk from those that involve *substantially greater* than minor increase over minimal risk. The distinction could lie in either the likelihood or the magnitude of the risk, or both.⁶⁰

While most procedures can generally be assigned to a particular risk category, policymakers or IRBs may place the same procedure in a higher risk category when it is performed on a vulnerable or physically infirm person. The serious medical, neurological, and psychiatric illnesses that give rise to impaired consent capacity may also place these individuals at an increased risk of harm and discomfort from research participation. For example, a lumbar puncture under local anesthesia may be considered a minor increase over minimal risk for healthy individuals, but more than a minor increase over minimal risk for acute care patients because of their physiological condition. For patients who are unable to express discomfort or pain or otherwise communicate their wishes once enrolled, research participation for individuals with cognitive impairments may involve added risk. Thus, for research involving adults lacking consent capacity, the Task Force recommends that IRBs carefully consider the type, probability, and degree of risk associated with the procedures as it would affect the target population.

2. Difficulties in Applying Risk Levels

Different IRBs, which are charged with evaluating risk in research protocols, may differ in their application of the standards for categorizing risk. For example, in pediatric research, there is evidence that IRBs inconsistently apply the three risk categories.⁶¹ One possible reason for this phenomenon stems from the lack of a federal definition of minor increase over minimal risk or of more than a minor increase over minimal risk, which results in IRBs subjectively interpreting the standard.⁶²

⁶⁰ For example, one might assume that a lumbar puncture with local anesthesia risks substantial and prolonged pain for three months in 10% of cases is no more than slightly greater in and of itself than the risks ordinarily encountered, and carries with it no greater than a remote possibility of substantial or prolonged pain. Thus, an IRB may categorize this procedure as involving no greater than a minor increase over minimal risk. On the other hand, consider three other procedures: Procedures A, B, and C. Procedure A, which risks the same pain for four months in 15% of cases, might be deemed as involving only slightly greater than a minor increase over minimal risk. Procedure B risks the same pain for twenty months in 10% of cases, and Procedure C risks the same pain for three months in 75%; both of these cases might be deemed as involving substantially greater than a minor increase over minimal risk. Procedures A, B, and C would all entail risk greater than a minor increase over minimal risk. However, with sufficient prospect of benefit and with appropriate safeguards, an IRB might be more likely to approve a study using Procedure A because the incremental risk is only marginal and not substantial.

⁶¹ Seema Shah et al., *How Do IRBs Apply the Federal Minimal Risk and Benefit Standards for Pediatric Research?* 291 JAMA 476, 478 (2004).

⁶² *Id.*, at 479.

The lack of clarity for the meaning of “daily life” in the definition of “minimal risk” gives rise to further difficulties in applying risk levels.⁶³ Specifically, conceptual confusion exists concerning whether it applies to healthy persons or to the specific population who will be studied in the research protocol. Commentators caution against allowing the exposure of an ailing research population to greater risks in research based on the assumption that these ill individuals are subjected to more risk in their daily lives than the average healthy person and therefore may routinely undergo invasive medical procedures.⁶⁴ Many scholars and policymakers have also asserted that risk should be indexed by the daily life of normal, healthy adults, which has the benefit of being a consistent standard and one that uses risks and experiences familiar to most persons, such as those encountered while driving a car or crossing the street.⁶⁵ This “objective” standard would avoid exploiting individuals in unfortunate circumstances;⁶⁶ however, for research involving a vulnerable population, it is essential that the risk estimate take into account the special vulnerabilities of participants who have physical impairments, are unable to express discomfort, or otherwise have difficulty communicating their wishes.

Some commentators claim that IRBs implement the minimal risk standard too cautiously, rejecting protocols that present a reasonable level of risk. Conversely, IRBs may implement the minimal risk standard too liberally, approving research that may pose an unhealthy amount of risk.⁶⁷ In addition, IRB members may rely on personal experiences and familiarity with certain activities rather than characteristics that directly correlate with risk when assessing protocols.⁶⁸ They may need more clarification on how to determine risk categories for experimental protocols, independent of their belief in the value of the study being contemplated.

While risk ceilings may be necessary for some human subjects research involving the cognitively impaired, bright-line cut-offs are only appropriate in limited circumstances; otherwise innovative research that may entail significant risk but also possess great promise may never be performed, thus hindering research breakthroughs that may greatly assist individuals who are similarly situated in the future. However, the Task Force recommends that such innovative research should only be approved for individuals who have first explored all available treatment and research options and failed to receive any therapeutic benefit, and for those without any other known treatment or research options available.

⁶³ Under the Common Rule, research may be characterized as minimal risk if “[t]he probability and magnitude of harms or discomforts anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychologic examinations or tests.” 45 C.F.R. § 46.102(i).

⁶⁴ Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 10; David Wendler, *Protecting Subjects Who Cannot Give Consent – Toward a Better Standard for “Minimal” Risks*, 35 HASTINGS CTR. REP. 37, 38 (2005).

⁶⁵ David Wendler et al., *Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit*, 294 JAMA 826, 827 (2005); Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 10.

⁶⁶ Wendler, *Protecting Subjects Who Cannot Give Consent – Toward a Better Standard for “Minimal” Risks*, *supra* note 64, at 38.

⁶⁷ Wendler, *Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit*, *supra* note 65, at 827.

⁶⁸ *Id.*

Other commentators have advocated abandoning the tripartite scheme altogether, and replacing it with a comprehensive list of procedures categorized by risk level.⁶⁹ Such an approach would clarify the specific risk level for any given procedure and would help ensure consistency in reviewing similar research protocols across institutions. However, because risks may vary across populations, it may be problematic to consistently categorize specific interventions. In addition, as science and medicine evolve, it would be difficult to assure that such a list remains up to date.

Although the tripartite risk scheme presents difficulties in application, it remains the most recognized and most used method to classify risks levels. These three major risk levels, particularly if one refines the degrees of the range of risks which are more than minor increase over minimal risk, are appropriate for IRBs and researchers to use.

3. Weighing Risks vs. Benefits

One of the core functions of an IRB is to review and approve studies that present a reasonable balance of potential benefits to risks. The Task Force recommends that for all human subjects research, the risk level should be minimized wherever possible to achieve the research objective. Although risk may never be eliminated completely in some studies, the Task Force recommends that procedures should be in place to assure an appropriate level of care for participants, including personalized attention to ensure safety and the use of required medical and therapeutic procedures where appropriate.

The Task Force recommends that IRBs carefully examine the extent or amount of any claimed potential direct benefit in relation to any harmful side effects. Although a research protocol may be represented as offering a potential direct benefit, studies that present potential negative side effects – particularly those that present a high likelihood of frequent or significant negative side effects – may exceed any positive outcomes. IRBs should pay attention to the distinctions between studies in which there is: (1) a high likelihood of a rare, yet minor harm, (2) a low (but not negligible) likelihood of a frequent, yet minor harm, or (3) a low (but not negligible) likelihood of a rare, yet significant harm. Particularly in the latter two of these sorts of situations, the benefits of a study may be outweighed by potential risks, and IRBs should be encouraged to move forward with caution. Exaggerating the degree or likelihood of the potential direct benefit and downplaying negative consequences can unfairly encourage a potential participant or surrogate decision-maker to provide consent to participate in a research protocol.

It may be difficult for an IRB to ascertain with precision the risks and benefits of a research protocol. In carrying out the task of evaluating research protocols, the Common Rule instructs that the “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”⁷⁰ Accordingly, the Task Force recommends that IRBs examine all of the risks and benefits of a study as a whole in the risk-benefit analysis.

⁶⁹ See, e.g., Rebecca Dresser, *Research Involving Persons with Mental Disabilities: A Review of Policy Issues and Proposals*, in NAT’L BIOETHICS ADVISORY COMM’N. RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY COMMISSIONED PAPERS VOL. II. (1999), at 21-22.

⁷⁰ 45 C.F.R. § 46.111.

In comparison to this more global analysis, some commentators have proposed employing a “component analysis,” whereby procedures with and without therapeutic benefit are individually scrutinized.⁷¹ An entire study would be deemed acceptable only when each component can be separately justified.⁷² While the analysis for procedures having the prospect of a direct benefit would mirror Subpart D of 45 C.F.R. 46, which involves additional protections for children,⁷³ procedures with no direct benefit would be justified by their potential to generate important scientific knowledge. Without component analysis, proponents argue that no-direct-benefit procedures could be “justified” by the presence of procedures that offer the prospect of direct benefit.⁷⁴ While component analysis has certain intrinsic appeal, it has yet to be tested properly, and has been criticized on a number of grounds.⁷⁵ In addition, some commentators have countered that, where participation overall is expected to be therapeutic, there is no compelling argument to bar research that includes “noninvasive medical technology, used daily in general medical practice ... [merely] because the interventions are not risk-free,” particularly where these techniques “present little risk and hold great promise for understanding and developing treatments” for illness.⁷⁶

4. Acceptable Risk-Benefit Ratios

The Task Force makes the following recommendations with regards to risk-benefit ratios for various research protocols involving cognitively impaired adults.

When research involves vulnerable individuals, the Task Force recommends that it is appropriate for IRBs to establish a lower ceiling for allowable risk or require a more favorable risk-benefit ratio for a protocol to be approved than they would for similar research involving non-vulnerable participants.⁷⁷ However, for research that may offer a prospect of direct benefit,

⁷¹ Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 11.

⁷² *Id.*

⁷³ 45 C.F.R. §§ 46.405 & 46.406. See Charles Weijer, *The Ethical Analysis of Risk*, 28 J.L. MED. & ETHICS 344, 358-360 (2000) (arguing that no risk-level cap is necessary in direct-benefit studies).

⁷⁴ Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 11.

⁷⁵ See Ezekiel Emanuel & Franklin G. Miller, *The Ethics of Placebo-Controlled Trials – A Middle Ground*, 345 N. ENGL. J. MED. 915, 915 (2001). For example, component analysis may focus too much on one specific type of harm. In placebo-controlled trials for antidepressants, some researchers consider depression-induced suicide the only meaningful harm, although other psychological and social harms may be relevant as well. Component analysis may also argue against a study based only on certain negative temporary effects – though long-term effects are promising – even though these negative effects may be reversible in the future.

⁷⁶ Stephan Haimowitz et al., *Uninformed Decisionmaking: The Case of Surrogate Research Consent*, 27 HASTINGS CENTER REP. 9, 13 (1997).

⁷⁷ An examination of state statutes reveals that most do not propose limitations on risk for research involving adults lacking consent capacity. Virginia, however, imposes a minor increase over minimal risk limit for surrogate consent to no-direct-benefit research but has no cap on risk exposure in direct-benefit studies. Va. Code Ann. § 32.1-162.18(B) (“A legally authorized representative may not consent to non-therapeutic research unless it is determined by the human research committee that such non-therapeutic research will present no more than a minor increase over minimal risk to the human subject.”). New Jersey’s statute allows all levels of risk in direct-benefit studies, so long as the IRB determines that “the risk is justified by the anticipated benefits to the subject and that the relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternative approaches.” With respect to no-direct-benefit research, New Jersey mandates that the protocol present no more

an IRB may allow a higher ceiling for allowable risk and allow a less favorable risk-benefit ratio for research.

For research that is categorized as offering no prospect of direct benefit, it may nevertheless be unclear whether the study has more than a negligible prospect of direct benefit or, if more than negligible, how much more;⁷⁸ clarity (or its absence) often depends on the current state of available scientific knowledge. For example, prospectively, the desired (and achieved) benefit in cases where deep brain stimulation has been administered to patients who have experienced traumatic brain injury and are in minimally conscious states is uncertain. Although the surgical procedure involves more than a minor increase over minimal risk, there are no other known clinical or research interventions that may improve the condition of these patients. Because deep brain stimulation is an innovative and risky procedure, with little data available, it would be arguably improper to suggest that the study holds out a prospect of direct benefit.⁷⁹ However, in the few instances in which the procedure has been performed, remarkable progress has been shown and such knowledge may be invaluable for future studies.⁸⁰

In such cases, where research offers no clear prospect of direct benefit, IRBs should determine whether the research is of “vital importance.” For research to be considered of vital importance, there must be clear and significant scientific evidence that the use of such a procedure or intervention presents a reasonable opportunity to further the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder.⁸¹ The IRB should carefully review the hypotheses of the study and antecedent evidence, such as data from animal studies, analogous research,⁸² or toxicity trial results, to evaluate whether the research is vitally important to the research population and will contribute knowledge about the disorder or condition.⁸³ Furthermore, the IRB should also examine the researchers’ therapeutic intent⁸⁴ and the purpose of the research study to determine whether the research is of vital importance and should be approved.

than a minor increase over minimal risk, and it may only be conducted where the participation of cognitively impaired individuals is required and the research relates to their condition. N.J.S.A. § 26:14-3(a)-(b).

⁷⁸ See Section VI.A.

⁷⁹ It may be prudent to separate therapeutic *intent* from therapeutic *benefit*, especially when the extent of potential benefit has not been established. See Joseph J. Fins, *A Proposed Ethical Framework for Interventional Cognitive Neuroscience: A Consideration of Deep Brain Stimulation in Impaired Consciousness*, 22 NEUROLOGICAL RES. 273, 274-275 (2000). It may be helpful for IRBs to use such considerations when attempting to establish the permissibility of studies with more than a minor increase over minimal risk in the absence of clear data regarding the study’s potential benefit.

⁸⁰ See, e.g., Nicholas D. Schiff et al., *Behavioral Improvements with Thalamic Stimulation After Severe Traumatic Brain Injury*, 448 NATURE 600, 600 (2007).

⁸¹ OHRP, *Secretary’s Advisory Committee on Human Research Protections (SACHRP), Appendix B*, <http://www.hhs.gov/ohrp/sachrp/sachrpltrtohhsecapdb.html> (last visited April 16, 2013).

⁸² In the context of this report, analogous research includes any previously performed studies with similar characteristics (i.e., research population or cognitive impairment examined) from which findings can be applied to the current study.

⁸³ OHRP, *Secretary’s Advisory Committee on Human Research Protections (SACHRP), Appendix B*, *supra* note 81.

⁸⁴ As noted above, therapeutic *intent* may be different from therapeutic *benefit*, especially when the extent of potential benefit has not been established. See Fins, *A Proposed Ethical Framework for Interventional Cognitive Neuroscience: A Consideration of Deep Brain Stimulation in Impaired Consciousness*, *supra* note 79, at 274-275 (arguing that the theoretical bases for hypotheses and (successful) preliminary work in animal models permits researchers to establish therapeutic intent).

The Task Force recommends that IRBs should require additional safeguards to ensure the safety and well-being of vulnerable participants.⁸⁵ Research involving higher levels of risk or diminished prospect of direct benefit may be permitted if additional safeguards, such as informed consent monitors (ICMs) and medically responsible clinicians (MRCs),⁸⁶ are in place to ensure that the rights and welfare of participants are protected. Thus, the Task Force recommends that both the degree of scrutiny by an IRB and the determination of the number and type of additional protections required should be unique to each study, and should be calibrated according to the risk level and the likelihood and significance of any direct benefit.

The Task Force recommends the following approach to oversee risk-benefit ratios for research involving individuals lacking consent capacity:

For research with minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies if the risks are reasonable in relation to the prospective benefits.

For research with minimal risk and *no prospect of direct benefit* to the participant, IRBs may approve such studies if the research is important to advance the scientific knowledge of a medical condition that affects the research population, and if the risks are reasonable in relation to such importance. Ethical issues related to research with minimal risk, with or without a prospect of direct benefit, are often manageable. IRBs, researchers, surrogate decision-makers, and potential participants should expect to resolve them without severely impeding research or unreasonably risking the participants' welfare, particularly when the beneficial prospect is more certain, or the benefit is expected to be more frequent or more significant.

For research with a minor increase over minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants. Such ratios are more favorable when the beneficial prospect is more certain or the benefit is expected to be more frequent or more significant. IRBs may recommend the use of ICMs, MRCs, or other additional safeguards.

For research with a minor increase over minimal risk and *no prospect of direct benefit* to the participant,⁸⁷ IRBs may approve such studies only if the research is vitally important to

⁸⁵ For a discussion on additional protections, *see* Section X.

⁸⁶ For a discussion on Informed Consent Monitors and Medically Responsible Clinicians, *see* Section X.A and X.B. An ICM is an individual not affiliated with the research study or institution who monitors the informed consent process and may also serve as an advocate for the potential participant and surrogate decision-maker during the recruitment process and possibly for the entire research study. An MRC is a licensed medical doctor skilled and experienced in working with the research population and is independent from the study.

⁸⁷ For children, 45 C.F.R. § 46.406 *allows* the following category of research:

Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

further the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population, and if the risks are reasonable in relation to the research’s “vital importance.”⁸⁸ Furthermore, IRBs may approve such studies only if they require mandatory rigorous procedures and oversight for enrollment and monitoring of participants through the use of safeguards, including an ICM and an MRC.

For research with a more than a minor increase over minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants. Such ratios are less favorable when the risk is substantially more than a minor increase over minimal risk. Such ratios are more favorable when the prospect of direct benefit is more certain, or the benefit is expected to be more frequent or more significant. IRBs should require the use of ICMs and MRCs.

For research with more than a minor increase over minimal risk and *no prospect of direct benefit* to the participant, IRBs may approve such studies in two circumstances: where the potential participants have a Research Advance Directive (RAD) *or* in special situations with notification to the Department of Health and use of a special review panel. These two scenarios are addressed in the following subsections.

(1) Use of Research Advance Directives (RADs)

The Task Force recommends that IRBs may approve studies in this risk-benefit category if all potential participants have, when they still had capacity, executed legally binding documents such as Research Advance Directives (RADs)⁸⁹ which explicitly state that they are willing to participate in this category of research. However, even if all participants have signed RADs, IRBs may approve such studies only if the research is of vital importance to the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population and/or those similarly situated. The IRB must determine that such risks are reasonable in relation to the research’s vital importance. Such risks are less likely to be reasonable if they are substantially, rather than marginally, more than a minor increase over minimal risk. Furthermore, IRBs may approve such

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- (a) The risk represents a minor increase over minimal risk;
 - (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and
 - (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

⁸⁸ Federal regulations regarding human subjects research with children permit this type of research protocol if, among other requirements, the IRB determines that the research is “likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition.” 45 C.F.R. § 46.406(c).

⁸⁹ For a discussion on RADs, *see* Section IX.B.

studies only if they require mandatory rigorous procedures and oversight for enrollment and monitoring of participants through the use of safeguards, including an ICM and an MRC.

(2) Notification to the Department of Health and Use of a Special Review Panel

However, there are limited circumstances where a research protocol may be considered for approval even where potential participants do not have RADs.⁹⁰ Thus, the Task Force recommends a second mechanism for IRBs to approve studies with more than a minor increase over minimal risk and no prospect of direct benefit. This alternative approval process consists of several steps: (1) IRB review, (2) Department of Health notification by the IRB and possible referral by the Department to a special review panel, and (3) IRB decision to approve or reject the research protocol.

For a protocol to be considered under this alternative process, the IRB must first examine whether the research is of vital importance to the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population, and if the risks are reasonable in relation to the research's vital importance. Such risks are less likely to be reasonable if they are substantially, rather than marginally, more than a minor increase over minimal risk. In addition, as noted above, although this type of research protocol must be labeled as offering no prospect of direct benefit, for some research participants, a remote possibility exists that they (or others similarly situated) may benefit from the research or from the knowledge gained.⁹¹ In such cases, the IRB must consider whether this remote possibility of benefit exists for potential participants, and weigh it against the potential risks of the protocol. Furthermore, the IRB should ensure that the study requires rigorous procedures and oversight for enrollment and monitoring of participants through the use of safeguards, including an ICM and MRC.

If the IRB concludes that the research is of vital importance to either current research participants and/or those similarly situated, that the risks are reasonable in relation to such vital importance, and appropriate safeguards are in place, such as the ICM and MRC addressed above, the IRB should notify the Department of Health. At the discretion of the Department of Health, the Department may: (1) reject the study (and thus the research could not be approved by the IRB), (2) approve the study (whereby the research could be approved by the IRB), or (3) convene a special review panel of experts⁹² who will examine the study and issue

⁹⁰ Because so few people have RADs, the Task Force concluded that an alternative mechanism for innovative research to be approved in very limited circumstances may be necessary.

⁹¹ See Fins, *A Proposed Ethical Framework for Interventional Cognitive Neuroscience: A Consideration of Deep Brain Stimulation in Impaired Consciousness*, *supra* note 79, at 274-275; see also Section VI.A.

⁹² One model for such a review panel is the federal 407 Review Children's Panels, which examines research protocols involving children that are otherwise not approvable because of their risk level. For children, research that is normally not approvable, but presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children:

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

recommendations to the IRB on whether the study should be approved. If the Department of Health decides that a special review panel must examine the protocol, after the special panel has made its recommendations, the Department should refer the protocol back to the IRB for review and the IRB will make the final determination based on the panel's recommendations, according to the process described below.

The special review panel should be comprised of experts knowledgeable about the conditions(s) or population(s) addressed by the research, to ensure that the reviewers are well-informed about the research topic and can provide meaningful commentary to aid in the IRB's decision-making.⁹³ While the Task Force acknowledges that the use of a special review panel may delay approval or the commencement of the study, this procedural process is important to safeguard participants. Furthermore, because only a small proportion of state-regulated research would fall into this risk-benefit category, the number of protocols that would be referred to a special review panel would likely be small. Thus, use of these panels would acknowledge the need for innovative research using the existing regulatory framework (i.e., respecting the IRB purpose and structure) and would also ensure that unethical research would not be conducted (supporting the IRB's opinion whether the protocol may be approved).

Where a protocol has been referred to a special review panel by the Department of Health,⁹⁴ the panelists should be required to provide a written report that will be publicly available, which will include a summary of the panel's reasoning, analysis, and recommendation to the IRB. The recommendations will advise the IRB to either reject or approve the study, and will include any modifications to the protocol. In the final step of this process, the IRB would then review the recommendations and decide to approve or reject the study.

The panelists should also forward their recommendations to the Department of Health for record keeping. The Department of Health should keep the individual panel members' recommendations on file and make them available to the public upon request, which would provide a historical record of the types of research studies considered by these panels. This information may help guide researchers as they design future studies, assist IRBs with their review and oversight process of this type of risk-benefit research, and promote transparency for

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

See 45 C.F.R. § 46.407.

⁹³ These experts would not be restricted to those residing in New York State. Instead, panelists would be selected for their knowledge and expertise in the particular area being studied.

⁹⁴ The Task Force recommends that the Department of Health provide the necessary resources to ensure that these special review panels are adequately supported.

the general public to maintain confidence in the oversight process of this type of unique research.⁹⁵

VII. CAPACITY ASSESSMENT

A. Defining Capacity

Consent capacity is the ability to demonstrate necessary levels of skill in four domains: (1) understanding; (2) appreciating the relevance of the information to oneself; (3) using information in reasoning about a decision; and (4) expressing a choice. Capacity may be impaired due to medical conditions or illnesses, chronic diseases, medication, or developmental cognitive impairment. Moreover, lack of capacity may be temporary or permanent, depending on the condition. Consent capacity is best understood as occurring along a continuum – it is not simply either present or absent. Although an individual may exhibit a degree of cognitive impairment, it should not be assumed that the person does not retain sufficient capacity to consent or decline to participate in all research studies.⁹⁶

Consent capacity has a complicated relationship to clinical diagnosis. Certain groups, such as those with dementia, schizophrenia, or mental retardation, are more likely to have impaired consent capacity than those with diagnoses which do not involve cognitive functioning, such as diabetes mellitus.⁹⁷ However, some individuals with a given diagnosis may retain

⁹⁵ Although some commentators have recommended the use of Central Review Committees where the local IRB does not have – or have access to – the resources or expertise to review any research protocol that involves a minor increase over minimal risk with no prospect of direct benefit, or involves more than a minor increase over minimal risk, with or without a prospect of direct benefit, such a committee would be too burdensome and costly to be effective. See e.g., Alice M. Mascette et al., *Are Central Institutional Review Boards the Solution? The National Heart, Lung, and Blood Institute Working Group's Report on Optimizing the IRB Process*, 87 ACAD. MED. 1710, 1713 (2012) (noting that start-up costs for creating a central IRB and unknown cost-efficiency were significant barriers to their implementation). Questions such as how often the committee would convene and how it would interface with local IRBs have been raised. Michelle Ng Gong et al., *Surrogate Consent for Research Involving Adults with Impaired Decision Making: Survey of Institutional Review Board Practices*, 38 CRIT. CARE MED. 2146, 2153 (2010) (arguing that central IRBs are appropriate for large multicenter studies, but not as appropriate for individualized institutions conducting their own research). Moreover, proponents have not yet addressed the matter of how long it will take for research protocols to be reviewed and approved, especially when time may be limited for some participants. Further, there remains the outstanding issue of whether researchers would report to either or both the local IRB and the central human research review committee. Finally, it has been argued that the use of a central review committee is contrary to the original purpose of IRBs, which is to ensure that decision-making occurs in a local context. Based on these considerations, the Task Force does not recommend the use of a central human research review committee. Instead, local IRBs – by incorporating the previous recommendations proposed by the Task Force – should conduct a comprehensive and thorough review of complex research protocols.

⁹⁶ Scott Y.H. Kim et al., *Assessing the Competence of Persons with Alzheimer's Disease in Providing Informed Consent for Participation in Research*, 158 AM. J. PSYCHIATRY 712, 712, 716 (2001); Celia B. Fisher et al., *Capacity of Persons with Mental Retardation to Consent to Participate in Randomized Clinical Trials*, 163 AM. J. PSYCHIATRY 1813, 1818-1819 (2006); Virginia D. Buckles et al., *Understanding of Informed Consent by Demented Individuals*, 61 NEUROLOGY 1662, 1665 (2003).

⁹⁷ See Barton W. Palmer et al., *Assessment of Capacity to Consent to Research Among Older Persons with Schizophrenia, Alzheimer Disease, or Diabetes Mellitus*, 62 ARCH. GEN. PSYCHIATRY 726, 731 (2005) (noting that patients with dementia and schizophrenia are more likely to exhibit deficits in consent capacity than either normal controls or patients with diabetes mellitus). See also David J. Moser et al., *Capacity to Provide Informed Consent for Participation in Schizophrenia and HIV Research*, 159 AM. J. PSYCHIATRY 1201, 1205 (2002), and Philip J.

consent capacity while others with the same disorder may not. In addition, a determination of impaired consent capacity may not be limited to individuals with psychiatric or neurological illnesses; patients such as those in critical care units or with chronic illness may also lack consent capacity. Accordingly, a participant's diagnosis cannot be a sole means of identifying those without consent capacity.⁹⁸

Furthermore, consent capacity among those who are cognitively impaired is likely to fluctuate over time and may be task-specific. The gradual loss of capacity is rarely linear; instead it may be periodic or cyclic in nature. For example, individuals with some psychiatric illnesses, such as bipolar disorder, have phases of clarity and lucidity between bouts of mania and depression. Participants with impaired consent capacity may experience oscillating levels of capacity during the course of a research study, which may alter how researchers assess capacity and when they obtain first-person or surrogate consent.

Determining whether a participant has sufficient consent capacity depends not only on the individual, but on the complexity of the research protocol and the risks and benefits associated with that protocol. Accordingly, the same patient may retain the capacity to consent to some protocols but not others. For a multifaceted study, particularly one that involves higher risk, it may be useful to ask a potential participant to demonstrate more rigorously that s/he grasps the effects of accepting or declining participation.

Thus, the threshold that distinguishes individuals who meet the consent capacity standard varies between research protocols.⁹⁹ The level of consent capacity should be appropriate to the complexity of the research, which includes the purpose and goals of the study and the risks and benefits involved. For instance, a drug placebo study that involves more than a minor increase over minimal risk may require an individual to have full consent capacity to participate; surrogate consent to participate may not be appropriate for such a study. Conversely, a modified level of consent capacity may be exhibited by a potential participant to enroll him/her in a study with minimal risk that offers a prospect of direct benefit.

Candilis et al., *A Direct Comparison of Research Decision-Making Capacity: Schizophrenia/Schizoaffective, Medically Ill, and Non-Ill Subjects*, 99 SCHIZOPHRENIA RES. 350, 350-351 (2008).

⁹⁸ In a study of consent capacity in cancer patients, the burden of symptoms, including pain and use of analgesics, was not strongly associated with consent capacity, in contrast to factors such as age, educational level, and cognitive function. David J. Casarett et al., *Identifying Ambulatory Cancer Patients at Risk of Impaired Capacity to Consent to Research*, 26 J. PAIN SYMPTOM MGMT. 615, 616, 621 (2003).

⁹⁹ For example, some clinicians assert that because obtaining informed consent from impaired adults in critical care settings is inherently challenging, informed consent should only be required when there is a high risk-benefit ratio, or the nature of such a treatment bears specifically on certain views that the patient is known to have. However, others argue that obtaining consent is still necessary to promote the rights and autonomy of patients. When there is such a lack of consensus on whether consent should be obtained, most experts suggest that informed consent should be obtained either directly or indirectly from the patient. Brigid Flanagan et al., *Protecting Participants of Clinical Trials Conducted in the Intensive Care Unit*, 26 J. INTENSIVE CARE MED. 237, 240-242 (2011).

B. Capacity Assessment

1. Tools for Screening and Evaluating Capacity

Establishing a suitable procedure to assess capacity for adults with impaired consent capacity is a significant challenge for researchers and IRBs. The Task Force recommends that researchers should take into account the likelihood of impaired consent capacity of the research population when selecting tools to screen and evaluate participants. When a study population has a low likelihood of cognitive impairment, a general screening may not be required, though researchers should take note of participants who reveal evidence of impaired capacity.¹⁰⁰ For a study involving participants with a significant possibility of impairment, researchers should document methods to determine capacity.

Current practices for screening and evaluating consent capacity vary in type and quality.¹⁰¹ Some researchers use non-standardized tests for assessing capacity, while others use clinical tools, such as the Mini Mental State Exam, which were not designed to assess, and correlate poorly with, consent capacity.¹⁰² Many researchers rely upon clinical interviews to evaluate consent capacity, but such interviews involve subjective elements and often result in different evaluators reaching diverse conclusions about a prospective participant's consent capacity.¹⁰³

More reliable methods for evaluating consent capacity have been developed in recent years. These tests fall into two basic categories: they either attempt to provide full assessment of all aspects of capacity yet are time-consuming, or they offer broad and simple assessments but lack detailed information. An example of a full assessment test is the MacArthur Competency Assessment Tool for Clinical Research (the MacCat-CR), a standardized tool that specifically measures capacity to consent to research.¹⁰⁴ Trained evaluators present information regarding a specific protocol to a potential participant, followed by questions designed to measure consent capacity. While the MacCat-CR provides a reliable appraisal of consent capacity, it takes fifteen to thirty minutes to administer to each individual, requires trained evaluators, and must be customized for every research protocol.¹⁰⁵ Shorter capacity assessment evaluations may be

¹⁰⁰ Physicians may, of course, incorrectly diagnosis a patient's consent capacity. See Laura L. Sessums et al., *Does This Patient Have Medical Decision-Making Capacity?* 306 JAMA 420, 425 (2011) (finding that 58 percent of physicians failed to identify incapacity in patients).

¹⁰¹ Scott Y.H. Kim et al., *Variability of Judgments of Capacity: Experience of Capacity Evaluators in a Study of Research Consent Capacity*, 52 PSYCHOSOMATICS 346, 351-352 (2011) (noting that because capacity assessment is a relatively new field, it may be appropriate to assess whether sufficient resources are available to those conducting assessments in high-stakes situations).

¹⁰² Edward D. Sturman, *The Capacity to Consent to Treatment and Research: A Review of Standardized Assessment Tools*, 25 CLIN. PSYCHOL. REV. 954, 964 (2005).

¹⁰³ Daniel C. Marson et al., *Consistency of Physicians' Legal Standard and Personal Judgments of Competency in Patients with Alzheimer Disease*, 48 J. AM. GERIATR. SOC. 911, 917 (2000).

¹⁰⁴ Laura B. Dunn et al., *Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments*, 163 AM. J. PSYCHIATRY 1323, 1331 (2006); Jason H.T. Karlawish et al., *Alzheimer's Disease Patients' and Caregivers' Capacity, Competency, and Reasons to Enroll in an Early-Phase Alzheimer's Disease Clinical Trial*, 50 J. AM. GERIATR. SOC. 2019, 2023 (2002). See also Sturman, *supra* note 102, at 957.

¹⁰⁵ Dunn, *Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments*, *supra* note 104, at 1329.

quickly and easily completed, but also have shortcomings.¹⁰⁶ One example of a rapid assessment tool is a three item questionnaire that takes little time to complete, does not entail extensively trained administrators, and is relatively accurate in identifying participants requiring further capacity assessments.¹⁰⁷ Other evaluators may employ a capacity scale, such as the University of California, San Diego Brief Assessment of Capacity to Consent, which consists of ten questions and may be performed in five minutes.¹⁰⁸ While short assessments may be quite accurate in determining general areas of capacity and incapacity, they also may be criticized on the grounds that they may overstate observed understanding and/or overlook lack of understanding, and that they frequently must be supplemented with additional tests to fully document consent capacity.¹⁰⁹

Selection of the best method for assessing consent capacity depends in part on the use researchers will make of the outcome. In cases where researchers seek to exclude all participants who lack consent capacity, briefer screening tools may suffice. For protocols in which researchers intend to enroll impaired individuals who require either remediation or other consent enhancement techniques to meet criteria for consent capacity, a more detailed evaluation tool, such as the MacCat-CR, may be most useful.¹¹⁰ In addition, proper use of the capacity evaluation tool may also be contingent on the inclusion or exclusion criteria of the research protocol. The Task Force recommends that researchers seeking approval of a study involving the cognitively impaired should provide the IRB with a description of the procedures and methods to be used for the initial capacity assessment, as well as how capacity will be monitored through the course of the study (if appropriate), and include information about who will conduct the assessment and his/her qualifications.

2. Timing of Capacity Assessment and Re-Evaluation

For studies that may call for a capacity assessment, it is critical that researchers consider the clinical status of a prospective participant when seeking to assess capacity, as cognitive abilities may improve as a patient stabilizes. The Task Force recommends that periodic re-evaluations of capacity may be appropriate, depending on the participants, the research protocol, and risk level involved. For example, a patient who exhibited capacity at the start of a research

¹⁰⁶ Dilip V. Jeste et al., *A New Brief Instrument for Assessing Decisional Capacity for Clinical Research*, 64 ARCH. GEN. PSYCHIATRY 966, 968 (2007).

¹⁰⁷ Palmer, *supra* note 97, at 730-731. The questionnaire prompts a participant to answer three questions regarding a hypothetical study: (1) What is the purpose of the study? (2) What are the risks of the study? and (3) What are the benefits of the study?

¹⁰⁸ Jeste, *supra* note 106, at 967.

¹⁰⁹ Palmer, *supra* note 97, at 728-732 (noting that decisional capacity consists of four dimensions, or subscales: understanding, appreciation, reasoning, and the ability to clearly communicate a choice. The researchers compared the values of the subscales across various capacity assessment tools. Following the three-item questionnaire, participants were evaluated by the more comprehensive MacCat-CR, and ultimately revealed significant correlation between the three-item and MacCat-CR subscales. However, while this correlation was fairly strong for the subscales of understanding, appreciation, and reasoning, it was weaker for expression of a choice. To this end, while the three-item questionnaire may be incorporated into the general consent process, it reveals weaknesses which may require the implementation of a more comprehensive capacity assessment.).

¹¹⁰ TRANS-NIH REPORT, *supra* note 40, at 7.

protocol may lose capacity completely over time, and as such the protocol should provide for periodic reassessment of the capacity of such participants.¹¹¹

In studies where surrogate consent to research is necessary to enroll adults lacking consent capacity, researchers should be mindful that since consent capacity can fluctuate over time, attempts should be made to take advantage of the opportunities where a current research participant experiences periods of lucidity to obtain first-person informed consent.¹¹² Sensitivity to the capacity levels of participants can assist researchers as they conduct ethical research with this vulnerable population.

3. Independent Evaluators of Capacity Assessments

It can be inappropriate for individuals affiliated with the research to perform capacity assessments. Some evaluators may be eager to identify potential participants as having consent capacity to enroll more participants and advance research goals, while others may be motivated to obtain consent from surrogate decision-makers who evaluators believe might have fewer objections to participation than the participants themselves. To prevent such occurrences, the Task Force recommends that, to avoid bias or the appearance of bias, researchers consider the use of “independent” evaluators (i.e., those not directly involved in the research) to determine the consent capacity of potential participants.¹¹³

The decision to use an independent assessment of capacity will depend upon the estimated capacity level of the potential participant(s), the amount of risk of the proposed research, and the complexity of the protocol.¹¹⁴ Some commentators have suggested that the physician who is primarily responsible for the prospective participant’s care – assuming the physician is not involved in the research – perform the independent capacity assessments.¹¹⁵ In addition, the evaluator may be required to have specialized expertise (i.e., appropriate professional training in the diagnosis of mental illness or developmental disability of the research population and the assessment of capacity).

Although the use of independent evaluators may be useful, IRBs, potential participants, and their surrogate decision-makers should be skeptical of the degree of “independence” these evaluators may actually possess. Even when evaluators have no prior relationship with researchers, they often receive compensation either in the form of direct payment or credit for assisting in the research – thus calling their “independence” into question – or may have a collegial relationship with the investigators which could color judgments by the evaluators. Despite these concerns, evaluators not associated with the research may provide an additional

¹¹¹ If researchers determine that a participant has lost capacity, it may be necessary to terminate the individual’s participation in the study or offer continued participation only with the re-consent of a surrogate decision-maker.

¹¹² For a discussion on informed consent, *see* Section VIII.

¹¹³ NBAC REPORT, *supra* note 50, at 22.

¹¹⁴ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 19. The IRB can make a determination of whether an independent capacity assessment is required on a study-by-study basis.

¹¹⁵ *Id.* The attending physician to the individual may be the Medically Responsible Clinician (MRC) that oversees the health and well-being of a participant during the course of a research study. For a discussion on the Medically Responsible Clinician, *see* Section X.B.

level of insurance against bias, particularly when the research carries an increased level of risk.¹¹⁶

Consequently, the Task Force recommends that researchers describe the qualifications of the person conducting the assessment and disclose to the IRB whether the person is affiliated with the study.

4. Notice to Participant and Opportunity for Review

Inaccurate capacity assessments can be harmful. An assessment that an individual lacks capacity may prevent an individual from making decisions for him/herself.¹¹⁷ Alternatively, the opposite may occur; an adult lacking consent capacity may be determined to be competent and may be vulnerable to research exploitation. In both instances, there should be procedures for providing notice to the potential research participant and, if necessary, the surrogate decision-maker, regarding the capacity assessment and opportunities for objection and review.

As part of a research protocol, the Task Force recommends that potential participants and/or surrogate decision-makers should be notified of a planned capacity assessment, as well as the results of the assessment and any consequences of a determination of incapacity.¹¹⁸ Providing notice promotes transparency by alleviating any concerns that an individual might be involved in research without the knowledge of the participant or surrogate decision-maker. It also demonstrates respect for the prospective participant by presenting an opportunity for the individual or his/her surrogate decision-maker to object to either the capacity assessment or the results of the evaluation. When capacity assessments are contested, the most ethical alternative may be to decline to enroll the individual in the research protocol. However, in some cases, alternatives short of non-enrollment could appropriately deal with any objection, such as a second capacity assessment.

Readily available review procedures allow individuals an opportunity to request further information or a second opinion where they or their surrogate decision-makers see fit. Furthermore, steps should be taken during the notification process to ensure that the results of the capacity assessment remain confidential and that the privacy of the individual is respected. Finally, the Task Force recommends that researchers inform patients of whether the results of the assessment will be entered into an individual's medical record.

¹¹⁶ Scott Y.H. Kim et al., *Proxy and Surrogate Consent in Geriatric Neuropsychiatric Research: Update and Recommendations*, 161 AM. J. PSYCHIATRY 797, 802 (2004). See also Elizabeth G. Nilson et al., *Clinical Ethics and the Quality Initiative: A Pilot Study for the Empirical Evaluation of Ethics Case Consultation*, 23 AM. J. MED. QUALITY 356, 357, 360 (2008) (suggesting that use of a formal ethics consult may helpfully incorporate the perspectives of the patient, research team, family, and any proxies into decision-making regarding the patient's status in the research study at crucial junctions in a research protocol (e.g., change in status, request to withdraw, etc.)).

¹¹⁷ Silverman, *Protecting Subjects with Decisional Impairment in Research*, *supra* note 32, at 12.

¹¹⁸ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 19.

VIII. CONSENT

A. Informed Consent Requirements

Informed consent is a fundamental tenet of ethically and legally acceptable human subjects research because it helps protect individuals from involuntary participation and exposure to risk. The Task Force recommends that informed consent should be obtained in a dynamic process, as part of a continued dialogue between the potential participant and the person presenting the research protocol. Asking detailed questions and having a discussion about the study with a knowledgeable person will help guide a potential participant in making a careful decision about whether research enrollment is appropriate (i.e., first-person decision-making). The focus of the informed consent process should be on this conversation and comprehension, rather than on the technicalities of the consent form.

The ability of cognitively impaired individuals to provide first-person informed consent differs widely but the Task Force recommends that it should always be sought when possible. Some members of this group may be unable to give consent while others still retain enough consent capacity to do so, especially with some assistance. Thus, the procedures for obtaining consent will vary depending on the consent capacity of the potential participant and the degree to which the potential participant can participate in the informed consent process.

The elements of informed consent consist of information, comprehension, and voluntariness.¹¹⁹ At a minimum, information about a research study should include a description of the procedures or interventions involved and their purposes, risks, and potential benefits; an opportunity for the potential participant to ask questions; and disclosure that withdrawal from the research is permitted at any time. Comprehension of the information ensures that a potential participant understands the research protocol – especially the risks and potential benefits – in such a way that a decision regarding enrollment can be made with confidence. Finally, the choice to participate in a study is only valid if the individual makes the decision free of coercion and undue influence. The Task Force recommends that informed consent be obtained before enrollment in a research study, but should also be re-obtained when circumstances significantly change the potential benefits or risks or harms, or when new scientific information becomes available.

In addition, the Task Force recommends, wherever possible, the use of a neutral discloser – a person not affiliated or having a vested interest in the research study – would help ensure that the information presented to a potential participant is impartial and objective.¹²⁰ However, if a member of the research team participates in the informed consent process, his/her role must be disclosed and additional care must be taken to ensure that the information is provided in a transparent, accurate, and unbiased manner.

¹¹⁹ THE BELMONT REPORT, *supra* note 6, at 7-8.

¹²⁰ This independent discloser is distinct from an Independent Consent Monitor (ICM). For a discussion of the role of an ICM, *see* Section X.A.

B. Improving Information Delivery

Potential participants with low levels of cognitive impairment may be able to give first-person consent with the help of certain remedial aids. These individuals may be able to understand the research protocol, including the purpose, risks, and possible benefits, when additional mechanisms are in place to aid them. Efforts to accommodate these individuals not only help strengthen the foundation of the research, but also reinforce researchers' commitment to respecting participants.

To increase the likelihood of comprehension sufficient for first-person consent, the Task Force recommends that researchers should attempt to provide information in a variety of ways, including repetition of information and presentation through question and answer formats, videos, or reading protocols aloud.¹²¹ It may be useful to explain the information slowly and calmly and to allow extra time for questions and discussion to aid in the informed consent process. Furthermore, incorporating nonverbal methods of information delivery, such as pictorial explanations, audio or visual computer presentations, or other forms of multimedia may also be useful.¹²² Researchers should make efforts to determine which information a participant does not comprehend – without conflating *confusion* with *dissent or assent*. Participants may need researchers to clarify any number of features of the research, including the purpose, methods, or duration of the study.¹²³ For complex research protocols, asking the potential participant to summarize the information may ensure that s/he has comprehended the essential aspects of the study.

The content and presentation of information in the consent form is also crucial to the promotion of informed consent. The terminology used in written materials is often difficult to comprehend, even by participants without cognitive impairment. Consent forms should be succinct, understandable, and aimed at conveying information effectively rather than seeking consent or primarily protecting against liability.¹²⁴ Efforts should be made to ensure that the most accurate and consistent vocabulary is maintained throughout the consent form.¹²⁵ Although IRBs routinely request that consent forms use non-technical language at a modest reading level, there is no guarantee that IRBs, researchers, and other involved parties either measure or adhere to proper levels of readability. Indeed, one study documented that consent forms approved by one state's department of mental health required a higher reading level than attained by many

¹²¹ See Moser, *supra* note 97, at 1202.

¹²² Laura B. Dunn et al., *Improving Understanding of Research Consent in Middle-Aged and Elderly Patients with Psychotic Disorders*, 10 AM. J. GERIATR. PSYCHIATRY 142, 147 (2002); James Flory & Ezekiel Emanuel, *Interventions to Improve Research Participants' Understanding in Informed Consent for Research*, 292 JAMA 1593, 1599 (2004).

¹²³ Allison R. Kaup et al., *Decisional Capacity and Consent for Schizophrenic Research*, 33 IRB: ETHICS & HUMAN RES. 1, 6 (2011).

¹²⁴ Some policy-makers recommend that researchers should, in fact, err on the side of over-disclosure to ensure an optimal level of transparency between the participant – or surrogate decision-maker – and the researchers. See Joseph J. Fins et al., *Ethical Guidance for the Management of Conflicts of Interest for Researchers, Engineers and Clinicians Engaged in the Development of Therapeutic Deep Brain Stimulation*, 8 J. NEURAL ENG'G 1, 4 (2011). However, such over-disclosure should not overwhelm a potential participant or surrogate decision-maker.

¹²⁵ *Id.*

enrolled participants, and the reading level needed to understand the forms increased as the risks of the study increased, making comprehension less likely when it was more crucial.¹²⁶

No single mode of providing information has proven to be the best way to improve informed consent across broad groups of individuals.¹²⁷ Consent enhancements can and should be adapted to the needs of the specific study and study population. The Task Force recommends that researchers should pay careful attention to information delivery and the accessibility of the information to improve the ability of potential participants (and surrogate decision-makers) to provide or withhold consent.

C. Assent and Dissent

Cognitively impaired adults who do not have the capacity to provide first-person informed consent may nevertheless retain sufficient capacity to understand some of the more basic concepts involved and provide assent – affirmative agreement – to participate in the proposed research. Therefore, to preserve the autonomy of potential participants who are capable of assent, the Task Force recommends that researchers must seek assent from such participants in addition to informed consent from a surrogate.¹²⁸

The mere absence of dissent is not equivalent to consent or even assent. Although the most preferable method to provide assent is through written or oral communication, these methods may not be possible for some adults lacking consent capacity. Assent or dissent may be expressed verbally, behaviorally, or emotionally. In such cases where the individual is capable of conveying assent, the researcher must seek a confirmatory response or gesture to communicate agreement to participate in the research. If the person capable of giving assent fails to do so – for example, is silent or uses no verbal, behavioral, or body language that conveys an opinion – this person cannot be enrolled in the study.

The Task Force recommends that where a potential participant is unable to provide or express assent, researchers must look for signs of dissent – the objection or resistance to participate in the study – both at the initiation of the study as well as once the participant is enrolled. Furthermore, if signs of dissent are present, the researcher may not enroll or allow continued participation of the individual in the study.

¹²⁶ Paul P. Christopher et al., *Consent Form Readability and Educational Levels of Potential Participants in Mental Health Research*, 58 PSYCHIATRIC SERV. 227, 230 (2007). In addition, the length of consent documents has increased over the past 20 years, which may prove cumbersome for some participants. Karl Desch et al., *Analysis of Informed Consent Document Utilization in a Minimal-Risk Genetic Study*, 155 ANN. INTERN. MED. 316, 321 (2011).

¹²⁷ Flory & Emanuel, *supra* note 122, at 1599.

¹²⁸ Some may argue that for individuals not capable of providing informed consent, there is no need to ask them for assent, and that instead use of surrogate consent is sufficient. However, this view ignores the fact that capacity is not an absolute; requiring assent from these participants allows them to retain a measure of control over their ability to make decisions. In addition, in years past, there was no requirement that impaired participants assent to research. Instead, impaired participants who objected to a surrogate enrolling them in research could rely upon judicial review to protect their right of refusal. However, judicial review is both time- and resource-consuming and removes the locus of authority from the potential participant. Requiring assent gives potential participants the swift and irrevocable right to decline to participate in research – without negating the option of judicial review if the participant so requests. It also guarantees that the surrogate decision-maker assists the participant in decision-making but does not usurp the participant's authority.

Dissent may be expressed orally, verbally, in writing, or via another type of communication. Forms that dissent may take will depend on each potential participant's degree of impairment. For individuals who are unable to clearly communicate an objection, gauging whether the participant is objecting to a procedure or intervention may be somewhat difficult; however, efforts should be made to determine the meaning of an individual's mood, behavior, or words.¹²⁹ At times, researchers may interpret an exclamation or gesture in anticipation of or in response to a research procedure as refusal to participate. Researchers should strive to differentiate between true signs of dissent and merely reflexive behavior that may ensue in the regular course of the intervention. For example, a non-reflexive wince in anticipation of a blood draw rather than one that occurs once a needle is inserted might indicate a participant's objection to the intervention.

D. Withdrawal from Research

Any participant who enrolls in a research protocol has the freedom to withdraw from the study without prejudice at any time, and this decision to withdraw should be respected. However, participants who have impaired consent capacity may be unable to express their preference to withdraw from the research. The Task Force recommends that researchers develop formal procedures to ensure that appropriate withdrawal mechanisms are available to the research population, that any withdrawal is accomplished with the least risk to the participant, and that any withdrawal, including the reason for it, is properly reported to the IRB.¹³⁰

Common reasons to withdraw a participant from research include: (1) the participant's consent capacity improves during the course of the study and s/he declines to continue; (2) the research does not hold out the prospect of direct benefit as described in the research protocol; (3) the research entails a higher level of risk than was initially anticipated; (4) the identification of unexpected adverse outcomes;¹³¹ or (5) continued participation in the research would detrimentally affect a participant's well-being. The withdrawal request may come from the participant, the surrogate decision-maker, or the researcher and should be honored, unless there are extraordinary circumstances that would preclude immediate withdrawal.¹³²

Several factors regarding participant withdrawal should be considered, depending on who is requesting the withdrawal and the reasons for it. If a participant or surrogate decision-maker expresses a desire to withdraw from the research, the researcher must honor the request and remove the individual from the study as safely as possible. If the researcher terminates an

¹²⁹ Betty S. Black et al., *Seeking Assent and Respecting Dissent in Dementia Research*, 18 AM. J. GERIATR. PSYCHIATRY 77, 81-82 (2010) (noting that aphasia can lead to a patient repeating the word "no" even when the patient may not mean "no." There may be discrepancies between a person's verbal, emotional, and behavioral indications of assent or dissent; in such cases, the researcher should seek the insight of an individual closest to the patient.).

¹³⁰ If financial remuneration or other forms of compensation to the participant or surrogate are involved, there should be procedures to address the effect of withdrawal on such compensation.

¹³¹ For a discussion on adverse outcomes, see Section X.D.3.

¹³² One example that would prevent immediate withdrawal from a research protocol would be if a participant in a clinical drug trial experiences negative side effects with a complete withdrawal of the drug. Instead, a gradual step-down of the dosage of the drug being tested would be necessary.

individual's participation in research, the researcher should explain to the participant and to the surrogate decision-maker the reasons for withdrawal, and where appropriate, other treatment options.

It may be possible in certain circumstances for a participant to withdraw from the primary interventional component of a study, but still continue with secondary research components or activities.¹³³ These activities may include obtaining data from the participant through verbal or physical interactions or obtaining identifiable private information about the individual through his/her records, medical providers, or social workers.¹³⁴ Thus, researchers may ask participants or surrogate decision-makers if withdrawal from such a study would include withdrawal from all aspects of the research or only from the primary interventional component of the study.

Finally, researchers must document the withdrawal of a participant. Such information may include: by whom the withdrawal decision was made; the reasons for the withdrawal; and whether the withdrawal was from all aspects of the research or just the primary interventional or procedural component.

IX. LEGALLY AUTHORIZED REPRESENTATIVES AND RESEARCH ADVANCE DIRECTIVES

When researchers are unable to obtain first-person informed consent from a potential participant, researchers may – depending on the nature of the study and the risk-benefit ratio – be permitted to enroll an individual using surrogate informed consent or according to a potential participant's research advance directive.

A. Legally Authorized Representatives (LARs)

1. Federal Law

Federal law clearly contemplates allowing surrogates to consent to research involving adults lacking consent capacity. The Common Rule provides that “no investigator may involve a human being as a subject in research . . . unless the investigator has obtained legally effective informed consent of the subject *or the subject's legally authorized representative.*”¹³⁵ The Common Rule defines an LAR as “an individual or judicial body *authorized under applicable law* to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research”¹³⁶

¹³³ OHRP, *Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues*, Sept. 2010, <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>.

¹³⁴ *Id.*

¹³⁵ 45 C.F.R. § 46.112 (emphasis added); 21 C.F.R. § 56.112 (FDA). *But see* 45 C.F.R. § 46.101(i) (waiver of the applicability of the Common Rule requirement for obtaining and documenting informed consent for research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the participants' medical condition and the unavailability of legally authorized representatives of the participants, no legally effective informed consent can be obtained).

¹³⁶ 45 C.F.R. § 46.102 (emphasis added).

This requirement has been interpreted to mean that the federal government will look to a state's formulation of LAR to determine which, if any, surrogates are authorized to consent to research conducted in that state. The federal government will recognize a state's definition of LAR if it is enshrined in statute, regulation, case law, or other legally-binding authority.¹³⁷ However, non-binding guidelines are insufficient.¹³⁸ In states that do not provide a definition of or a standard for selecting an LAR, it is arguable that federally funded research involving those who cannot provide informed consent should not occur, except in very limited circumstances.¹³⁹

Importantly, federal policy does not require that a state authorize an LAR specifically for the purpose of research.¹⁴⁰ Instead, where a state has authorized certain individuals to consent to an intervention for the purpose of treatment, federal policy will recognize that authority and allow those individuals to consent to the same interventions for the purpose of research.¹⁴¹ Federal policy does not explicitly require that an intervention hold out the prospect of direct benefit to the participant – or allow the intervention to be characterized as routine health care due to the likelihood of benefit – in order for a surrogate to have the authority to consent to enrollment.¹⁴² It is unclear whether and to what extent federally regulated research requires adherence to the other parts of a state health care statute beyond its surrogate hierarchy, such as

¹³⁷ OHRP, Human Research Protections Frequent Questions, *Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject?* <http://answers.hhs.gov/ohrp/questions/7264> (last visited July 16, 2012) [hereinafter OHRP, *LAR Frequent Questions*]. In addition to statutes, case law and official opinions from state Attorneys General have been deemed sufficient evidence of state policy permitting surrogate consent to research. See, e.g., Letter from Dr. Kristina C. Borrer, Compliance Oversight Coordinator at OHRP, to Dr. Donald C. Harrison, Senior Vice President and Provost for Health Affairs, University of Cincinnati & Dr. Elliot G. Cohen, Senior Executive Officer, University Hospital, Inc. et al. (Feb. 5, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/feb02i.pdf; Letter from Robert J. Meyer, Compliance Oversight Coordinator at OHRP, to Dr. Donald E. Wilson, Dean, School of Medicine, University of Maryland, Baltimore (Feb. 4, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/feb02f.pdf (acknowledging the University's reliance on the State's Health Care Decision Act and a legal opinion from the state Attorney General to authorize LAR consent to research).

¹³⁸ See, e.g., SIIIDR RECOMMENDATIONS, *supra* note 14, at 13. OHRP has also made clear that institutional guidelines alone cannot provide a basis for determining who may serve as an LAR in the absence of state law. See Letter from Dr. Kristina C. Borrer, Compliance Oversight Coordinator at OHRP, to Dr. Nathan Kase, Interim Dean, Mount Sinai School of Medicine (May 7, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/may02a.pdf.

¹³⁹ These circumstances include where the participant has an advance directive that addresses the research situation. Duly executed research advance directives would be honored in New York State, and will be discussed further in Section IX.B.

¹⁴⁰ Some states have passed legislation that specifically address and authorize surrogate consent to research. See e.g., Cal. Health & Saf. Code § 24178 (2010) (California), Va. Code Ann. § 32.1-162.18 (2010) (Virginia), and N.J.S.A. § 26:14-3 (2010) (New Jersey). See also John M. Luce, *California's New Law Allowing Surrogate Consent for Clinical Research Involving Subjects with Impaired Decision-Making Capacity*, 29 INTENSIVE CARE MED. 1024, 1025 (2003), and Ellen R. Saks et al., *Proxy Consent to Research: The Legal Landscape*, 8 YALE J. HEALTH POL'Y L. & ETHICS 37, 44-5 (2008).

¹⁴¹ OHRP, *LAR Frequent Questions*, *supra* note 137; see also Letter from Carol J. Weil, OHRP Division of Compliance Oversight, to Dr. Fawaz T. Ulaby, Vice President for Research, University of Michigan, Ann Arbor (Feb. 11, 2002), http://www.hhs.gov/ohrp/detrm_lettrs/YR02/feb02n.pdf (acknowledging the University's reliance on applicable statute to authorize surrogate consent to research).

¹⁴² *But see* Coleman, *Research with Decisionally Incapacitated Human Subjects*, *supra* note 45, at 756; Saks, *supra* note 140, at 54 (noting one OHRP letter suggesting that allowing health care surrogates to consent to research participation may be most appropriate where the research presents a prospect of direct benefit, but not actually setting such a limit).

the methods for determining capacity or the procedures for handling objections to determinations of incapacity or appointments of surrogates.¹⁴³

2. New York Law: Public Health Law Article 24-A

New York Public Health Law Article 24-A unambiguously allows reliance on LARs for human subjects research in its discussion of informed consent, referring to “the legally effective knowing consent of an individual *or his legally authorized representative . . .*”¹⁴⁴ Similarly, it states elsewhere that, “[i]f the human subject be otherwise legally unable to render consent, such consent shall be subscribed to in writing *by such other person as may be legally empowered to act on behalf of the human subject.*”¹⁴⁵

However, Article 24-A does not provide a statutory definition of, or hierarchy for, these LARs. In addition, neither the legislative history of Article 24-A nor documents contemporary with its passage shed light on who the Legislature contemplated to serve the role of LAR, including whether a surrogate decision-maker in the health care or other contexts would qualify to make decisions for participation in research. At the time of its enactment, family members routinely served as surrogates for consent to treatment¹⁴⁶ and possibly for research participation decisions, but such authority was informal and not pursuant to codified law. Given the paucity of statutes governing health care decision-making in existence during the time Article 24-A was proposed and enacted (1967-1975), and that at that time, the concept of diminished consent capacity was usually focused on individuals with mental illness or those adjudged to be “incompetent,” the Legislature may have been referring to certain Mental Hygiene laws – specifically, Articles 77 and 78 – that required a court to make affirmative findings about a person’s capacity and to appoint surrogate decision-makers.¹⁴⁷ Again, however, there is no

¹⁴³ See, e.g., Coleman, *Research with Decisionally Incapacitated Human Subjects*, *supra* note 45, at 760 (noting that the federal regulations are “silent on the substantive standards” an LAR must apply). Arguably, a health care statute requiring an LAR to use a “best interest” standard when deciding to enroll a person in research could not apply in the research context where the protocol holds out no prospect of benefit to the participant.

¹⁴⁴ N.Y. Pub. Health Law § 2441 (emphasis added).

¹⁴⁵ N.Y. Pub. Health Law § 2442 (emphasis added). Article 24-A clearly envisions that research involving adults lacking consent capacity will take place, requiring “the consent of the [review] committee and the commissioner [of health] . . . with the relation to the conduct of human subjects research involving minors, *incompetent persons, mentally disabled persons* and prisoners.” N.Y. Pub. Health Law § 2442(2) (emphasis added).

¹⁴⁶ The enactment of Article 24-A in 1975 pre-dates New York’s Do Not Resuscitate (DNR) Law, N.Y. Pub. Health Law Art. 29-B (effective 1987, but now applicable only in mental hygiene facilities); the Health Care Proxy statute, N.Y. Pub. Health Law Art. 29-C (effective 1990); the Health Care Decisions Act for Persons with Mental Retardation/Developmental Disabilities; N.Y. Surr. Ct. Proc. Act. § 1750-b (effective 2002); and the Guardianship statute, N.Y. Mental Hyg. Law Art. 81 (effective 1993). While the Durable Power of Attorney statute was enacted prior to 1975, it does not allow for most health care decision-making. See N.Y. Gen. Oblig. L. Art. 5, Tit. 15 (§ 5-1501) (effective 1964); see also 1984 Op. N.Y. Att’y Gen. 58 (No. 84-F16) (“A durable power of attorney may not be used to delegate to an agent generally the authority to make health care decisions on behalf of an incompetent principal. However, a durable power of attorney may be used to delegate specifically to an agent the responsibility to communicate the principal’s decision to decline medical treatment under defined circumstances.”).

¹⁴⁷ See N.Y. Mental Hyg. Law Art. 77, *repealed by* N.Y. Mental Hyg. Law Art. 81 (effective 1993); N.Y. Mental Hyg. Law Art. 78, *repealed by* N.Y. Mental Hyg. Law Art. 81 (effective 1993); see also Pub. Health Law § 2803-c(3)(j). Specifically, former Mental Hygiene Article 78 allowed courts to appoint a “committee of the person” or a “committee of the property” upon a finding of incompetence. N.Y. Mental Hyg. Law Art. 78, *repealed by* N.Y. Mental Hyg. Law Art. 81. Similarly, former Article 77 allowed courts to appoint conservators upon a finding by clear and convincing evidence that a person was unable to manage his/her affairs. N.Y. Mental Hyg. Law Art. 77

definitive indication that the Legislature had any specific law in mind at the time that would direct the hierarchy for LARs.

To date, neither the Legislature nor the Department of Health has explicitly specified the individuals who would be considered “legally authorized” to consent to research on behalf of an adult lacking consent capacity.¹⁴⁸ Consequently, although research involving adults lacking capacity to consent is legal on the conditions set forth in Article 24-A, it has been unclear who may serve as a research LAR.

3. New York Law: Family Health Care Decisions Act

Prior to the enactment of the Family Health Care Decisions Act (the FHCDA) in 2010, New York law did not generally statutorily authorize surrogate decision-making for health care on behalf of patients who lacked capacity unless the patient had previously appointed a health care proxy or was the subject of a guardianship proceeding.¹⁴⁹ The FHCDA filled much of this gap by creating a statutory framework for decision-making and providing a surrogate hierarchy for health care decision-making for such patients, with respect to treatment in specific health care settings.¹⁵⁰ The FHCDA authorizes surrogates to make decisions about “health care,” which it

(governing appointments of conservators), *repealed by* N.Y. Mental Hyg. Law Art. 81. While Article 77 was intended to bestow only powers over the conservatee’s property and associated decisions, over time, it was amended and interpreted to encompass personal decisions as well. *See* Dale L. Moore, *The Durable Power of Attorney as an Alternative to the Improper Use of Conservatorship for Health-Care Decisionmaking*, 60 ST. JOHN’S L. REV. 631, 642 (1986). *But see In re Grinker*, 77 N.Y.2d. 703 (1991) (invalidating this interpretation and finding that a conservator did not have the power to make the personal decision to place a conservatee in a nursing home).

¹⁴⁸ As addressed in the following section (IX.A.3), the New York State Legislature did not expressly apply the FHCDA to human subjects research, although federal law and policy permits the importation of the state health care surrogate hierarchy at least for federally-regulated human subjects research that offers prospect of direct therapeutic benefit. Moreover, this is not to suggest that the Department of Health has never attempted to address the concept of surrogate consent to research. Among other efforts, the Department of Health commissioned an advisory work group to study the issue, which released a draft report for public comment in 1998. *See* 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26.

¹⁴⁹ More specifically, New York law provided for surrogate decision-making for health care for three main categories of incapable adult patients: (i) patients who had previously appointed a health care agent pursuant to New York’s Health Care Proxy Law, *see* N.Y. Pub. Health Law Art. 29-C; (ii) persons who had a court-appointed guardian under Mental Hygiene Law Article 81, provided the guardianship order conveyed health care decision-making authority, *see* N.Y. Mental Hyg. Law § 81.22 (8); and (iii) persons with mental retardation or developmental disabilities who had a court-appointed guardian under Surrogate Court Procedure Act Article 17-A, *see* N.Y. Surr. Ct. Proc. Act § 1750-b. New York also has other surrogate decision-making laws for specific categories of health care decisions, *see, e.g.*, the DNR law, N.Y. Pub. Health Law Art. 29-B (governing decisions about cardiopulmonary resuscitation), and N.Y. Pub. Health Law § 4301(2) (governing decisions about anatomical gifts).

¹⁵⁰ N.Y. Pub. Health Law Art. § 29-cc (2010). *See* Robert Swidler, *New York’s Family Health Care Decisions Act: The Legal and Political Background, Key Provisions and Emerging Issues*, 82 N.Y.S. BAR J. 18 (2010). The limitation of the FHCDA to certain health care settings has significant implications for the impact of the FHCDA on research, particularly because the Act does not extend to care conducted in physician’s offices. Currently the FHCDA authorizes surrogate decisions only for treatment in hospitals, nursing homes, and hospice programs. N.Y. Pub. Health Law § 2994-b. Arguably, then, the surrogate’s authority is similarly limited to decisions regarding research in hospitals, nursing homes, and hospice programs. Upon the FHCDA’s passage, the New York State Legislature instructed the Task Force to “consider whether the FHCDA should be amended to apply to health care decisions in [other] settings.” 2010 N.Y. Laws Ch. 8, § 28(2). In December 2010, the Task Force submitted to the Legislature a proposal that the FHCDA be extended to allow surrogate decision-making for hospice care. New York State Task Force on Life and the Law, *Recommendations Regarding the Extension of the Family Health Care*

defines as “any treatment, service, or procedure to diagnose or treat an individual’s physical or mental condition.”¹⁵¹ The statute requires appointed surrogates to make patient-centered decisions based on the patient’s wishes, and where his/her wishes are not reasonably known, a patient’s “best interests.”¹⁵²

The FHCDA was not specifically drafted to govern surrogate consent to research,¹⁵³ and the Legislature did not expressly contemplate its use in the research context. However, the extent to which the FHCDA may authorize surrogates to consent to research participation on behalf of those lacking consent capacity is implicated because of the overlap between health care and research and, for federally regulated research, the authority conferred upon the “legally authorized representative.”

For non-federally regulated research, the FHCDA appears to authorize surrogate decisions for enrollment in protocols that offer a prospect of direct benefit to participants, where it can fairly be considered to be health care (as defined in the FHCDA). However, it is unclear whether the FHCDA allows for surrogate decision-making to research that holds out any lesser prospect of direct benefit. This approach arguably preserves consistency with the purpose of a surrogate in the treatment context: to allow consent to interventions that represent either the wishes or the best interests of the individual, with the goal of improving the person’s condition. Moreover, the FHCDA does not remove the Article 24-A requirement of Commissioner of Health approval for research with this vulnerable population.

Interestingly, however, while the FHCDA has only a modest impact on state regulated research, it has an immense impact on the legality of federally regulated research involving patients who lack consent capacity. By authorizing surrogate consent to treatment and providing the concomitant surrogate hierarchy, the FHCDA greatly expanded the potential for the cognitively impaired to participate in federally regulated research in New York. As previously described, federal policy governing a majority of federally regulated research involving human subjects permits researchers to use state health care decision-making LAR hierarchies for consent to research involving the cognitively impaired. Thus, while the FHCDA is not a

Decisions Act to Include Hospice (Dec. 22, 2010), available at http://www.health.state.ny.us/regulations/task_force/docs/2010-11-30_recommendations_regarding_the_extension_of_family_health_care_decisions_act.pdf. These recommendations formed the basis for legislation passed in July 2011. 2011 N.Y. Laws Ch. 167. In April 2013, the Task Force submitted to the Legislature that the FHCDA be extended to allow surrogate decision-making to other Medicare and/or Medicaid-certified and State-licensed community-based settings that opt-in to the oversight mechanisms of the FHCDA. New York State Task Force on Life and the Law, *Recommendations for Extending the Family Health Care Decisions Act to Medicare and/or Medicaid-Certified and State-Licensed Agencies, Programs, and Settings* (June 3, 2013).

¹⁵¹ N.Y. Pub. Health Law § 2994-a(12); N.Y. Pub. Health Law § 2994-a(14) (defining “health care”).

¹⁵² N.Y. Pub. Health Law § 2994-d(4). The decision must be patient-centered, and the statute sets forth the considerations an LAR must make when determining a patient’s best interests: “consideration of the dignity and uniqueness of every person; the possibility and extent of preserving the patient’s life; the preservation, improvement or restoration of the patient’s health or functioning; the relief of the patient’s suffering; and any medical consideration and such other concerns and values as a reasonable person in the patient’s circumstances would wish to consider.” For a discussion of the best interest standard, see Section IX.A.5.b.

¹⁵³ See *supra* note 140 for examples of state statutes that specifically address research involving adults lacking consent capacity.

research statute and does not define the term LAR explicitly for research purposes, it provides an applicable statutory definition of a surrogate for federally regulated research.¹⁵⁴

4. Selecting an LAR to Provide Surrogate Consent to Research

Neither the New York Legislature nor the Department of Health has directly addressed who should act as a research LAR for the cognitively impaired. If future rules are to be promulgated regarding who may consent, different considerations and standards of decision-making should apply to research than to treatment.¹⁵⁵

Other proxy statutes, such as laws related to health care, Do Not Resuscitate orders, and organ donation, often contain hierarchies of decision-makers that descend in priority, usually beginning with the person considered to be closest (by kinship or intimacy level) to the impaired individual. These hierarchies designate a person that the incapacitated individual might have chosen to be an LAR and who would make decisions in accordance with the person's values, preferences, and interests.

While hierarchies are practical for determining who may serve as an LAR, not all LARs are ethical equivalents, particularly when considering research enrollment decisions. Because LARs listed in a hierarchy often will have varying degrees of kinship, intimacy, and understanding of the wishes of the impaired individual regarding research participation, it is important to consider the relationship between the LAR and the potential participant with respect to the type of research and risk level involved.¹⁵⁶ An LAR who has a close relationship with the impaired individual would be the most familiar with whether s/he would choose to participate in research and under what circumstances. Thus, the Task Force recommends that IRBs and researchers consider limiting the classes of LAR(s) who are authorized to provide surrogate consent to research.¹⁵⁷ The riskier the research protocol and more remote the prospect of benefit, the closer (by kinship or intimacy level) the LAR should be to an individual to be imbued with authority to consent to the impaired individual's participation in the study. For example, while all classes of LARs might be allowed to consent to research that involves minimal risk and offers the prospect of direct benefit, IRBs might only permit a certain LAR class to consent to research that involves no prospect of direct benefit and involves a minor increase over minimal risk, or more than a minor increase over minimal risk.

¹⁵⁴ If researchers in New York proceed using the surrogate hierarchy found in the FHCDCA pursuant to federal policy, the following individuals in each class will have the authority to consent to research for an individual who lacks decision-making capacity, in order of priority: (1) a guardian authorized to make health care decisions; (2) a spouse, unless legally separated from the participant, or the domestic partner; (3) an adult child; (4) a parent; (5) an adult sibling; and (6) a close friend. N.Y. Pub. Health Law § 2994-d(1).

¹⁵⁵ See, e.g., Gong, *supra* note 95, at 2153.

¹⁵⁶ Although it may not be fair to assume that all appointed health care proxies or family members of impaired individuals would have a close relationship, or conversely, to assume that a close friend would not know the individual as well as a family member, such generalizations may be useful to an IRB when limiting which class of LAR(s) may consent to research involving a significant level of risk with little prospect of direct benefit.

¹⁵⁷ However, not all individuals who fall within the same class of an LAR hierarchy claim (for example, multiple brothers and sisters) may be familiar with and understand the wishes and values of their cognitively impaired sibling.

The Task Force recognizes that, ideally, an individual should select an LAR before s/he no longer has consent capacity, using a legally binding document, such as a health care proxy or research advance directive.¹⁵⁸ The Task Force prefers such appointments because it assumes that the appointed LAR has a close relationship with the individual and that a discussion regarding research preferences has taken place. In some cases, a cognitively impaired adult may retain sufficient capacity to choose a research proxy – a research agent – to make research decisions on his/her behalf, but lack capacity to consent to research participation him/herself.¹⁵⁹ Strict procedural mechanisms and safeguards, similar to those used in a health care proxy designation appointed while the individual has consent capacity, should be in place to ensure that an individual’s appointment of a research agent using a legally binding document is an unbiased and free choice.¹⁶⁰

For research that has no prospect of direct benefit and involves either a minor increase over minimal risk, or more than a minor increase over minimal risk, it is ethically inappropriate to allow for a surrogate appointed through an institutional or judicial mechanism (i.e., a court-appointed guardian with no prior relationship to the potential participant) to provide surrogate consent. Because these court-appointed LARs often do not have a close personal relationship with the impaired individuals, it would be difficult to accurately act upon their wishes and preferences, and a more cautious approach to research enrollment is reasonable. However, it might be acceptable for IRBs to permit these LARs to consent to research that offers a prospect of direct benefit, depending on the risk level of the study, for these cognitively impaired individuals.

The Task Force also recommends the placement of restrictions on who may serve as an LAR to ensure that participants are adequately protected. For example, the number of research participants for whom an LAR can serve should be reasonably limited to make certain that his/her duties to them are not compromised. If a physician is appointed as an LAR, s/he should not simultaneously continue to act as the treating physician to the participant because of a potential conflict of interest. In addition, individuals who are involved in the conduct of a particular research study should not serve as an LAR for a participant in the study, although an exception may be made for where a close familial or other relationship exists between the two individuals.

5. Research Enrollment Decision-Making

a. Distinction between Research and Treatment

Appreciating the ethical and practical distinction between clinical treatment and research is crucial to understanding the implications of permitting an LAR to make decisions about

¹⁵⁸ For a discussion on research advance directives, see Section IX.B.

¹⁵⁹ Scott Y.H. Kim, *The Ethics of Informed Consent in Alzheimer Disease Research*, 7 NATURE REV. NEUROLOGY 410, 412 (2011) (noting that a significant number of Alzheimer’s disease patients may be able to appoint an LAR in a “concurrent” rather than advance directive).

¹⁶⁰ Such procedures may include a witness(es) and documentation for the appointment. See Scott Y.H. Kim, *Preservation of the Capacity to Appoint a Proxy Decision Maker: Implications for Dementia Research*, 68 ARCH. GEN. PSYCHIATRY 214, 215-216 (2011) (discussing appointment of a proxy where a person does not retain sufficient enough capacity to consent to the protocol itself).

research enrollment. The differences are reflected in both the professional relationship between the physician/researcher and the patient/participant and the goals inherent in each endeavor.¹⁶¹

In the physician-patient relationship, care is tailored to meet the specific needs of the patient. In the researcher-participant relationship, interventions are prescribed according to a protocol and often are not altered to meet the needs of each individual. Although physicians and researchers often engage in research to improve patient care, individualized medical care has the goal of improving a particular patient's health, while the primary goal of research is obtaining scientific information, such as drug safety and efficacy data, to benefit a class of individuals.¹⁶² For potential participants and their LARs who are considering research enrollment in connection with their medical care, the involvement of the treating physician, regardless of whether s/he is conducting the research or merely providing a referral, can also create confusion about the line between treatment and research.¹⁶³

This distinction is arguably less problematic when a protocol offers the potential for direct benefit to a participant, rendering it more akin to treatment. In the research context, direct benefit refers to a real or perceived positive value related to a person's health or welfare.¹⁶⁴ Where research offers a prospect of direct benefit, researchers believe that there is a reasonable probability that participants will receive some therapeutic benefit.¹⁶⁵ However, while participants in clinical research may receive a therapeutic benefit from their participation, providing these benefits is not the *purpose* of the research.¹⁶⁶

Even in some prospect-of-direct-benefit studies, the prospect of receiving that benefit may be very remote, or there may be significant drawbacks to participation that outweigh the possible benefit. Similarly, just because a study is characterized as a prospect-of-direct-benefit study, benefits may not manifest for each participant, or they may not be manifest to the same degree. It has been argued that usage of common scientific techniques, such as randomization, placebos, and double-blind procedures, may be incompatible with the principles of personalized clinical treatment.¹⁶⁷ Moreover, to preserve the scientific integrity of the research protocol, participants may be asked to do a variety of things unrelated to the potentially beneficial intervention. For example, a participant may be subjected to daily blood draws or weigh-ins for the purpose of data gathering.

¹⁶¹ See, e.g., THE BELMONT REPORT, *supra* note 6, at 4.

¹⁶² *Id.*

¹⁶³ *Id.*

¹⁶⁴ THE BELMONT REPORT, *supra* note 6, at 8.

¹⁶⁵ In contrast, research seeking only to gain generalizable knowledge about the condition or treatment being studied is characterized as no-direct-benefit research.

¹⁶⁶ Franklin G. Miller & Donald L. Rosenstein, *The Therapeutic Orientation to Clinical Trials*, 348 N. ENGL. J. MED. 1383, 1383 (2003).

¹⁶⁷ Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 HASTINGS CENTER REP. 20, 20 (1987). Others have argued that these techniques, such as the process of randomization – where participants are randomly assigned to receive either the investigational intervention, the standard treatment, or possibly a placebo – do not pose harm to participants because clinical trials are done only in instances of “clinical equipoise.” See Coleman, *Research with Decisionally Incapacitated Human Subjects*, *supra* note 45, at 752-3.

Research and treatment overlap to the greatest degree in instances when the trial is done in “clinical equipoise” (i.e., research where there is genuine disagreement among expert clinicians about the relative merits of an investigational intervention and the available alternatives for a given population).¹⁶⁸ But even in clinical equipoise, the “equipoise assessments are based on the expected benefits and burdens of the interventions for the overall patient population,” rather than on particular individuals’ unique characteristics.¹⁶⁹ Therefore, characterizing a prospect-of-direct-benefit study as “health care” is often inaccurate.

Thus, because research is distinct from treatment, a decision to enroll a participant in research may require different considerations, procedures, and standards than those for treatment decisions.¹⁷⁰ The Task Force recommends that these considerations should include the potential risks and benefits, the likelihood and extent the participant will receive any direct benefit or experience any adverse consequences/risk, and whether any potential benefits from research offered to the participant could instead be obtained in the treatment context.

b. Decision-Making Standards and Responsibilities of LARs

The Task Force recommends that LARs make research enrollment decisions using the prior expressed wishes regarding research when the potential participant still had capacity, if known. While these previously conveyed preferences might not have been expressed in writing (i.e., through a health care proxy document or research advance directive) and might not be legally binding, the LAR should honor them, especially when the instructions are specific with regard to types of research or levels of risk.¹⁷¹

In most instances involving research participation, however, the wishes of a cognitively impaired individual are unknown. In such cases, the Task Force recommends that LARs use one of two decision-making standards: the “best interest” standard and the “substituted judgment” standard.¹⁷² In the health care context, the best interest standard traditionally applies to treatment where a patient’s preferences are unspecified; it requires a surrogate to choose the option that will both respect the patient and provide the most benefit to him/her.¹⁷³ The standard, as applied

¹⁶⁸ Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 N. ENGL. J. MED. 141, 141 (1987).

¹⁶⁹ Coleman, *Research with Decisionally Incapacitated Human Subjects*, *supra* note 45, at 752-3.

¹⁷⁰ Additionally, many commentators and ethicists argue that the difference between treatment and research warrants distinct ethical analyses. *See, e.g.*, Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials*, 33 HASTINGS CENTER REP. 19, 21 (2003).

¹⁷¹ *See* Joseph J. Fins et al., *Contracts, Covenants and Advance Care Planning: An Empirical Study of the Moral Obligations of Patient and Proxy*, 29 J. PAIN SYMPTOM MGMT. 55, 65 (2005) (suggesting that in some cases, in the treatment context, discretionary – or covenantal – moral judgment made by a surrogate was superior to strict adherence to prior wishes, especially in situations when the initial instruction was to “do everything” and the prognosis was unfavorable. Thus, instead of adhering to narrow notions of patient self-determination, surrogates were able to make nuanced and contextually informed moral judgments.).

¹⁷² In a review of laws applicable to surrogate consent to research, in the treatment context, at least twenty-nine states require that surrogates employ the substituted judgment standard when making decisions, while seven states rely on the best interest standard. Saks, *supra* note 140, at 49.

¹⁷³ *See* Jeffrey T. Berger, *Is Best Interests a Relevant Decision Making Standard for Enrolling Non-Capacitated Subjects Into Clinical Research?* 37 J. MED. ETHICS 45, 46 (2011) (noting that the best interests standard tends to be conservative, as conventional social norms such as “being free of distressing physical symptoms [and] being free of excessive psychological, emotional and existential suffering, etc.” are usually judged against potential harms and risks. There is no normative standard by which to weigh the various benefits over potential harms.).

to human subjects research, necessitates that the risks/burdens and potential benefits of research participation are reasonable in relation to each other. A best interest determination should take into account the following: (1) the necessity of the research study and potential for generalizable knowledge it presents; (2) the potential short- and long-term effects on the physical or mental well-being of the participant; (3) the expected degree of physical pain or discomfort, psychological distress, and any loss of dignity that may result from participation; (4) the individual's prognosis; (5) whether there are alternatives to research participation available; and (6) the risks, benefits, and potential side effects of participation as compared to those of standard treatment.

The best interest standard is often difficult to apply in the research setting. It may be most appropriate to use when the research offers a prospect of benefit, because these protocols are more analogous to interventions in the treatment context. In some circumstances, procedures and interventions offered in research are the best, equivalent to other, or the only therapeutic option available; therefore participation in the study can be judged to be in the best interest of the individual. However, while these studies may present a prospect of direct benefit, this benefit is not guaranteed, and thus the notion of best interest would less certainly support participation. In addition, it is arguable that in many cases, especially where there is no prospect of direct benefit to participants or the potential benefit is very remote, research participation is never in the best interest of the individual.

For research that offers no prospect of direct benefit, it may be more appropriate for an LAR to employ the substituted judgment standard, which relies on the known and/or presumed values and beliefs of the cognitively impaired individual to guide an LAR in the decision. An LAR may rely on relevant factors that indicate an individual's beliefs about medical research, including prior research participation, general statements or attitudes about research participation, or specific moral or religious convictions that may have some bearing on medical research. In considering these factors, an LAR can make a reasonably assured estimate of whether the individual would choose to enroll in research.

Finally, the Task Force recommends that LARs should understand their continued role and responsibilities associated with the research protocol and should be available on an ongoing basis once an individual is enrolled in a study. LARs should be accessible to both participants and researchers to oversee participation, communicate with researchers and the participant, and make additional decisions where necessary. It is imperative that the LAR serves as an advocate for the participant by ensuring that the LAR remains consistently involved in the study.

6. Correcting the Therapeutic Misconception

Even where participants and LARs are informed that any benefit of a research protocol is theoretical or uncertain or that there may not be any direct benefit, people often mistakenly believe otherwise. The perception that the participant will receive personalized medical care or a direct therapeutic benefit from the study is a phenomenon known as the therapeutic misconception.¹⁷⁴

¹⁷⁴ Charles W. Lidz & Paul S. Appelbaum, *The Therapeutic Misconception: Problems and Solutions*, 40 MED. CARE V55, V57 (2002). In addition, unrealistic optimism may interfere with an individual's ability to apply information

Similarly, research participants and LARs underestimate the risks, and overestimate the benefit, of participating in medical research. Data have shown that “research subjects systematically misinterpret the risk-benefit ratio of participating in research because they fail to understand the underlying scientific methodology.”¹⁷⁵ The misconception often is due to an individual’s belief that physicians and other medical professionals always provide care that is most appropriate for the individual.

Accordingly, the Task Force recommends that researchers should make scrupulous efforts to ensure that potential participants and/or their LARs fully understand the difference between the goals of research (i.e., generalizable knowledge) and the goals of clinical care (i.e., improving the health of an individual), as well as the risks and benefits to participating in the specific research protocol. Researchers should provide information about the study in a way to help dispel the therapeutic misconception. Such techniques may include: (1) utilizing clear and succinct language on the informed consent document listing the protocol’s risks and stating clearly that the protocol is not intended to benefit the participant; (2) using questionnaires to verify that the participant does not misconstrue the intent of the research; (3) disclosing any financial remuneration, specifically for referring an individual to a research protocol or that a researcher receives from a research sponsor,¹⁷⁶ and (4) paying individuals for their participation, which could serve as a reminder that the research is principally for the benefit of others rather than the participant.¹⁷⁷ In addition, it may be helpful to have a neutral discloser, or a person who is not a member of the individual’s health care treatment team, to explain the research protocol to eliminate the possibility that the credentials and authority of the researcher¹⁷⁸ or the health care provider may inappropriately influence the participant or LAR.¹⁷⁹

7. Conflicts of Interest for LARs

Potential conflicts of interest may arise between LARs and the individuals they represent. Although most LARs will make research participation decisions that are the most appropriate for cognitively impaired individuals, there may be some instances where an LAR does not make decisions that respect the individual’s preferences or values. For example, studies have revealed that LARs may enroll an individual in research to ease those LARs of their care-giving

regarding the risks and benefits of a research protocol realistically to him/herself. See Lynn A. Jansen et al., *Unrealistic Optimism in Early-Phase Oncology Trials*, 33 IRB ETHICS & HUM. RES. 1, 5 (2011).

¹⁷⁵ Appelbaum et al., *False Hopes and Best Data*, *supra* note 167, at 22.

¹⁷⁶ Rebecca Dresser, *The Ubiquity and Utility of the Therapeutic Misconception*, 19 SOC. PHIL. & POL’Y 271, 278 (2002).

¹⁷⁷ David Shore, *Ethical Issues in Schizophrenia Research: A Commentary on Some Current Concerns*, 32 SCHIZOPHRENIA BULL. 26, 27 (2006). However, financial remuneration is often misconstrued to be a direct benefit. See Section VI.A.

¹⁷⁸ Appelbaum et al., *False Hopes and Best Data*, *supra* note 167, at 23 (suggesting that because researchers are often already sufficiently burdened by the intricacies of the recruitment process (in that they need to gain participants’ trust and ensure cooperation), it may not be in their or the study’s self-interest to fully explain all of the risks of the study, or to disabuse a potential participant of therapeutic misconception. While researchers should discuss the therapeutic misconception with potential participants, researchers are unlikely to provide information willingly regarding whether the research may – or may not – benefit the participants. A neutral discloser may mitigate this issue.).

¹⁷⁹ Appelbaum et al., *False Hopes and Best Data*, *supra* note 167, at 23-24.

obligations or as a means to otherwise benefit themselves, rather than the participant.¹⁸⁰ Other studies uncovered a willingness by some LARs to consent to research on behalf of a patient in which neither they themselves, nor – as they believed – the person for whom they acted, would participate.¹⁸¹

In addition, many studies offer financial remuneration for participation in a study, often to offset an individual's time, expenses, and possible discomfort related to the research.¹⁸² In such cases, there is concern regarding who actually has access to the funds received – the cognitively impaired participant or the LAR who authorized the research participation. Although any compensation may be presented directly to the participant, there is no assurance that the participant, rather than the LAR, has control of his/her finances. The promise of compensation might influence an LAR to downplay or ignore the risks of the research protocol and approve enrollment, although such participation might not be beneficial to the impaired individual.

Again, the Task Force recommends that LARs should not consider financial remuneration to be a direct benefit. In addition, to prevent undue inducement to consent to research, the Task Force recommends that researchers should examine whether the LAR is the true beneficiary of any funds received or if the enrollment of the potential participant might alleviate the burdens of caring for the individual.

8. Objections to the Appointment of an LAR

Allowing a potential participant to reject the appointment of an LAR for research purposes promotes autonomy and self-determination. Opposition by a potential participant to the appointment could be evidence not only of objection to the person appointed as the LAR, but also of refusal to participate in the protocol at all.

Furthermore, potential surrogate decision-makers could object to another person being appointed as the designated LAR. Where two or more persons fall within the same class of an LAR hierarchy and claim to be an individual's LAR,¹⁸³ IRBs should require the research team to encourage the parties either to attempt to agree who will serve as the LAR or make the research enrollment decision together. In the event that potential LARs cannot decide who should serve or whether an individual should be enrolled in research, the Task Force recommends that researchers should not permit LAR consent to research for this potential participant and (to avoid "LAR shopping") should not seek surrogate consent from another individual who could be appointed as an LAR.¹⁸⁴

¹⁸⁰ Dresser, *Research Involving Persons with Mental Disabilities*, *supra* note 69, at 34-35.

¹⁸¹ *Id.*, at 35.

¹⁸² The financial remuneration should not exceed reasonable "reimbursement" standards to forgo the possibility of an undue inducement to participate. Compensation for the time and possible risks involved must be fair, but should not encourage participants to take unreasonable and unhealthy risks or encourage LARs to provide surrogate consent.

¹⁸³ For example, adult siblings of a cognitively impaired individual are in the same "class" within the LAR hierarchy.

¹⁸⁴ Other states have addressed the issue of conflicts between surrogates in the research context. In New Jersey, California, and Virginia, where there is a conflict between qualified surrogates in the same class of an LAR hierarchy, consent to research cannot be obtained and the participant will not be enrolled. *See* N.J. STAT. ANN.

While the FHCDA surrogate hierarchy provides distinct classes in order of preference¹⁸⁵ by which an LAR may be selected, any qualified person who falls under one of the categories may be appointed to be the LAR, provided that no one in a class higher in priority objects.¹⁸⁶ In the case of research, when there is an objection to the LAR appointment by a member in a different class or to whether enrollment should occur, the Task Force recommends that under no circumstances should the cognitively impaired individual be enrolled.

B. Research Advance Directives

A research advance directive (RAD) provides an individual's instructions for future research participation should s/he lose consent capacity and is similar to an advance directive for clinical treatments (i.e., living wills).¹⁸⁷ A research agent appointed by an RAD is not the same as a designated research agent who is appointed when an impaired individual does not have the capacity to consent to research but does retain enough capacity to appoint a person to be a surrogate decision-maker for research.¹⁸⁸ An RAD reflects a non-cognitively impaired individual's autonomy by establishing his/her wishes about participation in certain types of prospect-of-direct-benefit and no-direct-benefit research, acceptable risk levels, and other specific concerns regarding research. This document would not go into effect and empower the designated research agent unless there was a determination that the individual has lost consent capacity. Even if a potential participant has an RAD, consent by his/her research agent would still be needed since an RAD would not substitute for surrogate consent. In addition, an RAD does not absolve a researcher or the research agent from the responsibility of safeguarding the well-being of the individual participating in research. However, the document does guide a research agent when trying to determine if an individual would have consented to a particular research protocol before consent capacity was impaired.

RADs could prove particularly useful in two noteworthy circumstances. First, an RAD could offer explicit directions regarding the individual's desire to participate in research. Individuals may decide that they never wish to participate in research, irrespective of any research protocol protections that may be provided; or they may specify limitations on types of research or particular risk levels.¹⁸⁹ RADs may also indicate that an individual may be willing to participate in research that involves a significant level of risk with no prospect of direct benefit.

26:14-5(c)(1); CAL. HEALTH & SAFETY CODE § 24178(d)(1); and VA. CODE ANN. § 32.1-162.18(A). In these states, a lower-ranked surrogate cannot challenge or override the decision of someone higher on the list.

¹⁸⁵ The assumption is made that an individual in a higher "class" has a closer intimacy level with the adult patient who lacks decision-making capacity. For example, the spouse or domestic partner of the individual is in a higher class than the category of a close friend.

¹⁸⁶ Per the FHCDA, when there is an objection to the LAR appointment by another potential LAR candidate, the attending physician must refer the case to the facilities' ethics review committee, if it cannot be resolved. N.Y. Pub. Health Law § 2994-f(2)(b).

¹⁸⁷ Although advance directives typically only cover treatment decisions, it is possible to draft an advance directive to include research. The same person may be an incapacitated individual's health care proxy and research agent.

¹⁸⁸ For a discussion on a research agent appointed by a partially cognitively impaired individual, see Section IX.A.4.

¹⁸⁹ Palaniappan Muthappan et al., *Research Advance Directives: Protection or Obstacle?*, 162 AM. J. PSYCHIATRY 2389, 2389-2390 (2005) (finding that 13 percent of people who completed an RAD indicated an unwillingness to participate in any research in the event of a loss of decision-making capacity).

Second, RADs could help in studies in which fluctuating or deteriorating mental status is likely for participants. For instance, a study intended to follow individuals with early Alzheimer's disease over the course of several years may ask participants who possess consent capacity at enrollment to complete an RAD and select a research agent who would make research decisions if and when the participant loses consent capacity. Participants may also choose to include in the RAD that their participation in the study should terminate when they lose consent capacity or provide detailed information about other research in which they would be willing to participate.

Although RADs may provide a means to respect an individual's autonomy, strict adherence to the directive may not always be desirable. When completing the RAD, the person will likely lack adequate information to make a truly informed decision about not-yet-identified future research projects.¹⁹⁰ Individuals with consent capacity now may not be able to predict how they would experience research participation as a cognitively impaired participant. In addition, a research agent should be able to override an RAD where, although the directive permits participation in a type of study, participation becomes too onerous or threatens the participant's welfare.¹⁹¹

While there are benefits to using RADs for research, it would be a practical impossibility to require the execution of such directives for all adults who lack consent capacity for the purposes of research. Most adults in New York and across the United States do not have advance directives even for clinical treatment, let alone research, and these documents are particularly uncommon among ethnic minorities, the socio-economically disadvantaged, and those with lower levels of education.¹⁹² Given the infrequent use of clinical advance directives despite considerable encouragement, it is highly unlikely that RADs will gain a significant degree of popularity in the general population.¹⁹³ Furthermore, requiring that all potential research participants without consent capacity to have completed an RAD will bar most cognitively impaired individuals from participation in and access to potentially beneficial research.

Moreover, although RADs are useful in preserving individual autonomy and safeguarding rights and welfare in the research context, the scope and effects of many of these documents are subject to interpretation. RADs can never replace first-person informed consent for research participation and may only be beneficial in limited circumstances. For instance, participation in research that involves more than a minor increase over minimal risk with no

¹⁹⁰ See, e.g., Rebecca Dresser, *Mentally Disabled Research Subjects: The Enduring Policy Issues*, 276 JAMA 67, 69 (1996); Oldham, *supra* note 50, at 690.

¹⁹¹ See, e.g., American Geriatrics Society Ethics Committee, *Informed Consent for Research on Human Subjects with Dementia*, 46 J. AM. GERIATR. SOC. 1308, 1309 (1998).

¹⁹² Because of their relative rarity among the disadvantaged, advance directives have not proved to be an effective method of ensuring autonomy for those most in need of support. Faith P. Hopp & Sonia A. Duffy, *Racial Variations in End-of-Life Care*, 48 J. AM. GERIATR. SOC. 658, 661 (2000).

¹⁹³ Gina Bravo et al., *Advance Directives for Health Care and Research: Prevalence and Correlates*, 17 ALZHEIMER DISEASE & ASSOCIATED DISORDERS 215, 217 (2003) (finding that, in a survey of older adults in Quebec, 11.3 percent of individuals had discussed wishes pertaining to research with family members, while only 7.4 percent of individuals had committed to preferences in writing).

prospect of direct benefit would be permitted when those individuals have explicitly stated in their RADs that they are willing to be part of this type of research.

X. ADDITIONAL SAFEGUARDS FOR RESEARCH PARTICIPANTS LACKING CONSENT CAPACITY

Additional protections might sometimes be necessary to safeguard the rights of participants who lack consent capacity, particularly when a study involves a minor increase over minimal risk or more than a minor increase over minimal risk, and when there is no prospect of direct benefit to the participant. Such protective measures may include, but are not limited to: (1) independent consent monitors; (2) medically responsible clinicians; (3) state multiple project assurances; and (4) additional reporting requirements. These measures are addressed in turn below, and in Appendix B.

A. Independent Consent Monitor

By commonly accepted definitions, an ICM is an individual not affiliated with the study or research institution, who is designated by an IRB to monitor the informed consent process¹⁹⁴ – for example, when LAR consent is required. In some cases, this safeguard may provide additional protection for potential participants, because an ICM’s duties include ensuring that as a witness to the consent process, verification of valid consent is properly obtained.¹⁹⁵ An ICM provides confirmation that adults lacking consent capacity are enrolled in research protocols only when appropriate informed consent procedures are followed. In addition, an ICM may also confirm that LARs understand the goals and risks of the research by observing the informed consent process.¹⁹⁶

Furthermore, an ICM may provide independent assurance that an adult lacking consent capacity is enrolled in research only when there is sufficient evidence that such participation is consistent with the person’s preferences and/or interests. For example, if a potential participant has an RAD, the ICM could review the risk-benefit preferences documented therein to provide reasonable assurance that the individual would have authorized his/her participation in the proposed research. The ICM provides an important resource to ensure that the decision whether to enroll is independent and appropriate for the individual.

For some research protocols, an ICM may have a more active role as an advocate for the potential participant and LAR during the recruitment process and possibly for the entire research

¹⁹⁴ See NBAC REPORT, *supra* note 50, at 21; TRANS-NIH REPORT, *supra* note 40, at 9; MARYLAND ATTORNEY GENERAL REPORT, *supra* note 33, at A-5; Donald L. Rosenstein & Franklin G. Miller, *Ethical Considerations in Psychopharmacological Research Involving Decisionally Impaired Subjects*, 171 PSYCHOPHARMACOLOGY 92, 94 (2003); Committee on Assessing the System for Protecting Human Research Participants, Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Research Participants*, 164, Washington, DC (Daniel Federman et al., eds., The National Academies Press, 2002).

¹⁹⁵ NBAC REPORT, *supra* note 50, at 21.

¹⁹⁶ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 22; Henry J. Silverman et al., *European Union Directive and the Protection of Incapacitated Subjects in Research: An Ethical Analysis*, 30 INTENSIVE CARE MED. 1723, 1727 (2004).

study.¹⁹⁷ For example, although informed consent forms and descriptions of protocols provide information about the research, they are often complicated and may be overwhelming to potential research participants or LARs who are not familiar with research studies. In addition, some potential participants and their LARs may be intimidated by the medical research setting, or may feel uncomfortable making an enrollment decision because of their lack of understanding of research procedures.¹⁹⁸ To assist with this decision, and to provide emotional and technical support to potential participants and their LARs, it may be useful for an ICM to participate in the enrollment process.

The ICM may serve as a *resource* to help potential participants and LARs understand the potential risks and benefits and decide if enrollment in a research protocol would be appropriate. The ICM should be familiar with the clinical aspects of the research protocol, understand and be able to answer questions, especially those concerning risk-benefit information, in plain language. This person could also address additional concerns from participants and LARs during the course of the research study and may help a participant and his/her LAR decide whether continued participation is appropriate. For potential participants without consent capacity, an ICM should offer insight to the LAR as to whether or not the individual should be enrolled in a particular study while respecting the difficulty an LAR may face when making difficult decisions concerning the loved one.¹⁹⁹

The Task Force recommends that the role and responsibilities of an ICM may vary, from monitoring the informed consent process to advocating on behalf of potential and current research participants, and the degree of involvement of the ICM would be determined by an IRB. After reviewing the research protocol and the risk-benefit level involved, an IRB may determine the scope of responsibilities of an ICM.

Although use of an ICM is usually optional for minimal risk studies that do or do not hold a prospect of direct benefit to participants, the Task Force considers that there are several instances where an IRB should recommend or even require one for research to be approved. An IRB may *recommend* the use of an ICM when the research involves a minor increase over minimal risk and holds out a prospect of direct benefit. An IRB should *require* the use of an

¹⁹⁷ E. Haavi Morreim, *By Any Other Name: The Many Iterations of "Patient Advocate" in Clinical Research*, 26 IRB: ETHICS & HUM. RES. 1, 5 (2004). Research protocols at the National Institutes of Health/National Institute of Mental Health employ a Clinical Research Advocate, which is a hybrid of a traditional ICM and of an advocate for vulnerable research participants. These Clinical Research Advocates provide assistance to potential and current research participants by overseeing the informed consent process and also assess the surrogate decision-makers who may be involved in the process of informed consent. Mary Ellen Cadman, Presentation, *Human Subjects Protection Unit*, at Public Responsibility in Medicine and Research (PRIM&R) Conference 2008 (Nov. 18, 2008).

¹⁹⁸ NBAC REPORT, *supra* note 50, at 37.

¹⁹⁹ Ideally, an ICM would have experience serving as a surrogate decision-maker for a person who has had a similar disorder affecting consent capacity. Joseph J. Fins & Franklin G. Miller, *Enrolling Decisionally Incapacitated Subjects in Neuropsychiatric Research*, 5 CNS SPECTRUMS 32, 41 (2000) (proposing a matrix of individuals and perspectives, which would assist with enrollment decisions. In their model, an IRB could convene a Surrogate Decision-Making Committee (SDMC). The SDMC would consist of the potential subject's legally authorized representative (LAR) and attending physician (serving as an independent health care professional), the clinical investigator, and a research participant advocate who has experience working with and making decisions for an individual with a similar disorder, and would serve as a resource for the LAR during the decision making process, while also protecting the potential participant.).

ICM if the research entails a minor increase over minimal risk, but is a no-direct-benefit study. If a research protocol entails more than a minor increase over minimal risk, with or without a prospect of direct benefit, the IRB should also *require* the use of an ICM along with additional protections.²⁰⁰

B. Medically Responsible Clinician

Depending on the research study and risk level involved, use of a medically responsible clinician (MRC) for each participant may be a necessary safeguard to protect cognitively impaired individuals. An MRC is a licensed medical doctor skilled and experienced in working with the research population and is independent from the study. Ideally, this person should be the physician already attending to the participant's health care needs – who is not involved in the research – but an MRC may also be any qualified physician not affiliated with the research study. While the primary role of an MRC is to serve as an advisor to an individual or LAR regarding research participation, additional duties may include: (1) confirming that a participant provided assent to be enrolled in the research; (2) observing the individual for possible dissent to continued participation; and (3) monitoring the individual for any signs of harm as a result of research participation.²⁰¹ In addition, the MRC should notify the researcher and the participant's LAR if any information presents itself that is relevant to research participation.

The Task Force recommends that the use of an MRC may be optional, strongly recommended, or required (with or without additional protections), depending on whether the research offers the prospect of benefit and the level of risk involved. The use of an MRC should be *optional* for minimal risk studies that do or do not offer a prospect of direct benefit. However, an MRC is *strongly recommended* when the research involves a minor increase over minimal risk and holds out a prospect of direct benefit. An IRB should *require* an MRC for an approved no-direct-benefit study that involves a minor increase over minimal risk. Likewise, if the approved research protocol entails more than a minor increase over minimal risk and there is or is not a prospect of direct benefit, an IRB should *require* the use of an MRC along with additional protections. Thus, use of an MRC is an important safeguard for high risk studies because the physician acts as an active advocate for cognitively impaired individuals. The MRC serves as a mechanism to assure that the physical and emotional well-being of participants are looked after by an outside third party.

C. State Multiple Project Assurances

According to New York law, the consent of the Commissioner of Health is required for all non-federally regulated research involving “incompetent persons [and] mentally disabled persons,” regardless of the risk category.²⁰² However, to streamline the review process, the Task Force recommends that the Department of Health should develop multiple project assurances

²⁰⁰ See, e.g., Dave Wendler & Kiran Prasad, *Core Safeguards for Clinical Research with Adults who are Unable to Consent*, 135 ANN. INTERN. MED. 514, 519-520 (2001). However, as discussed above, only under limited circumstances would no-direct-benefit research with a high risk level be approved by an IRB.

²⁰¹ 1998 NEW YORK STATE WORK GROUP REPORT, *supra* note 26, at 21.

²⁰² N.Y. Pub. Health Law § 2444.

(MPAs)²⁰³ to ensure a timely and thorough review of research protocols by IRBs. An MPA is an assurance between the Department of Health and a research entity or institution that pledges that all members of the entity or institution will comply with human subjects research policies issued by the State.

When an MPA is appropriate, an institution should pledge that it will: (1) require all human subjects research protocols to be evaluated by an IRB and will be subject to continuing review; (2) provide a statement of principles that will be used to protect the rights and welfare of participants; (3) designate at least one IRB that will be responsible for oversight; and (4) create a system of documentation of procedures and reporting requirements.

The Task Force recommends the use of a State MPA to obviate the need for full case-by-case Commissioner/Department of Health review for research involving cognitively impaired individuals that involves minimal risk or a minor increase over minimal risk, with or without a prospect of direct benefit, and for research that involves more than a minor increase over minimal risk with a prospect of direct benefit. However, for research that involves more than a minor increase over minimal risk, *without* a prospect of direct benefit, a State MPA should not be a valid release from review by the Department of Health. In these cases, if an IRB concludes that the research is of vital importance to either current research participants and/or those similarly situated, that the risks are reasonable in relation to such vital importance, and appropriate safeguards are in place, the Department of Health may: (1) reject the study and the research could not be approved by the IRB, (2) approve the study and the research could be approved by the IRB, or (3) convene a special review panel of experts which will review the study and issue recommendations to the IRB on whether the study should be approved, and the IRB will make the final decision to approve or reject the protocol.²⁰⁴

D. Reporting Requirements

1. IRB Reporting Requirements to the New York State Department of Health

As discussed previously,²⁰⁵ while most research conducted in the State is federally regulated or overseen, there is a small portion of research that is not under federal purview. The Task Force recommends that research involving individuals unable to provide consent under Public Health Law 24-A should be subject to federal reporting requirements.²⁰⁶ These reporting requirements will promote accountability and transparency and may include, if appropriate, evaluations of capacity of participants, including the method(s) used to assess capacity; procedures used to identify LARs for surrogate consent to research; an overview of the risk-benefit analysis used; and a summary of various risk levels involved in approved protocols.

²⁰³ A State MPA would be like a Federalwide Assurance (FWA), a document filed with OHRP by an institution, which ensures that all of its human subject research activities, regardless of the funding source, will comply with the federal research protections provided in the Common Rule.

²⁰⁴ For a discussion on the special review panel, *see* Section VI.B.4.

²⁰⁵ *See* Section II.B.2.

²⁰⁶ Many states require additional oversight and reporting standards beyond the federal standards. At this time, the Task Force recommends that the federal standards serve as minimum standards for research that falls under N.Y. Pub. Health Law Art. 24-A.

Furthermore, the Task Force recommends that IRBs be required to report to the Department any violations of approved principles and policies which the institution has promulgated.²⁰⁷

2. Researcher Reporting Requirements to the IRB and to Participants/LARs

The Task Force recommends that researchers conducting studies under Public Health Law 24-A involving individuals unable to provide consent should be subject to federally-mandated reporting requirements and provide such documentation to the IRB. Under federal regulations, researchers are required to submit extensive documentation to an IRB as part of the review and approval process. Common documentation requirements include: (1) evidence of appropriate education training in human subjects research protection; (2) assessment of potential participants' capacity, including information on who conducted the assessments and how decision-making capacity was assessed; (3) procedures for re-evaluating a participant's capacity; (4) privacy protections to protect potential participants' information; (5) procedures by which the health and safety of participants were monitored during the course of the research, including appropriate consultation with the participant's LAR or MRC, if appropriate; (6) unanticipated adverse events involving risk to participants or others; and (7) reasons for withdrawal of a participant from the research study.²⁰⁸ In addition, the Task Force recommends that researchers should also disclose relevant information to potential participants and LARs of how the study will be ethically conducted to ensure that the rights and welfare of participants are protected.

Once the study is underway, the Task Force recommends that researchers should provide regular updates on the status of the participant and the general progress of the study to the participant and/or LAR. They should report any substantial concerns regarding an individual's participation to the LAR in ordinary language so that s/he remains fully informed. In addition, the researcher should remind participants and LARs of the availability of the researcher throughout the study to address any questions. Only with full disclosure to participants, LARs, and IRBs of the status and progress of the research, can all parties be confident that the study is being conducted in an ethical and safe manner.

3. Reporting of Adverse Events and Unanticipated Problems

The disclosure of adverse events²⁰⁹ and unanticipated problems²¹⁰ that result from research participation promotes transparency and may further protect the welfare of research

²⁰⁷ N.Y. Pub. Health Law § 2444(2).

²⁰⁸ See generally 45 C.F.R. §§ 46.109, 46.111, 46.116-17.

²⁰⁹ The Common Rule does not define or use the term "adverse event," nor is there a commonly used definition of the term. FDA regulations use "adverse event," (21 C.F.R. § 312.64), "adverse effect" (21 C.F.R. § 312.55), "adverse experience" (21 C.F.R. § 312.33), "unanticipated problems" (21 C.F.R. § 312.66), and "unanticipated adverse device effect" (21 C.F.R. § 812.3) interchangeably. See HHS, *Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection* (Jan. 2009), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf>.

²¹⁰ The Common Rule requires IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and to the federal government of, among other things, any unanticipated problems involving risks to participants or others, but it does not define such "unanticipated problems." See 45 C.F.R. § 46.103(b)(5).

participants.²¹¹ OHRP has suggested definitions of “adverse events” – which are not (in all cases) necessarily reportable to the IRB or federal agency – and “unanticipated problems” which must be reported; the definitions overlap but an occurrence might be either an adverse event or an unanticipated problem without being the other.²¹² While most adverse events are not unanticipated problems, and only some unanticipated problems are adverse events, only a small proportion of adverse events are unanticipated problems.

Because the severity of any given adverse event may range from minimal to serious, because the natural progression of an illness or condition under study will vary, and because the severity and frequency of anticipated problems inherent to the research will vary, IRBs should determine, based on the research protocol, which events would require immediate action by the researcher or institution. Any reasonable possibility that a protocol may have caused serious or life-threatening harm or death requires immediate reporting and attention by the researcher and IRB to provide any corrective or preventative action.

The Task Force recommends that for both IRBs and researchers, any non-federal research protocol should contain methods for the identification, management, and reporting of adverse events and unanticipated problems that may occur during the course of a research protocol, comparable to those contemplated by the federal Common Rule.²¹³

XI. TASK FORCE RECOMMENDATIONS: BEST PRACTICES BY IRBS AND RESEARCHERS, LARS, AND ACTIONS BY THE DEPARTMENT OF HEALTH

In developing these guidelines, the Task Force considered and declined to recommend legislation governing research involving individuals who lack consent capacity. It concluded that because existing law permits research involving this population, no statutory change is

²¹¹ As with many of the topics discussed in this report, although reporting of adverse events and unanticipated problems is an important component of human subjects research, these recommendations are not intended to emphasize the exceptionalism of this population, but to serve as a model for reporting adverse events and unanticipated problems.

²¹² OHRP has suggested that an “adverse event” is any untoward or unfavorable medical occurrence in a participant, including any abnormal sign, symptom, or disease, temporarily associated with the individual’s participation in the research, whether or not considered related to the individual’s participation in the research. Adverse events, other than the natural progression of the illness or condition which is the subject of the research, may be caused by equipment malfunction or error during the course of diagnosis or treatment of a participant, by a placebo, or by an interventional agent which is the subject of the research. Any negative effect, physiological, psychological, economic or social, ranging from minimal to serious, even death, may be an adverse event. In addition, OHRP has suggested that an “unanticipated problem” is any incident, experience or problem that is: (1) unexpected in terms of nature, severity, or frequency; (2) related or possibly related to participation in the research; and (3) suggests that the research places subjects or others at greater risk of harm, including physical, psychological, economic or social harm. OHRP, *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, <http://www.hhs.gov/ohrp/policy/advevntguid.html> (last visited April 16, 2013).

²¹³ The Common Rule requires institutions conducting federally funded research or operating under FWAs to establish procedures for adverse event reporting. 45 C.F.R. § 46.103(a) & (b)(5). The IRB assurance must include: “Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.” 45 C.F.R. § 46.103(b)(5). See also OHRP, *Guidance on Adverse Events*, *supra* note 212. N.Y. Pub. Health Law Art. 24-A does not require such reporting.

needed. The Task Force therefore identified approaches that comply with current law, including Public Health Law 24-A, to ensure ethical practices in research involving this vulnerable population.

The following section summarizes the key recommendations to IRBs, researchers, and legally authorized representatives (LARs), and actions by the Department of Health regarding the conduct of research in New York involving those who lack consent capacity already discussed in this report.

A. Responsibilities of IRBs

1. General Responsibilities

- a. An IRB must ensure that the least burdened population is utilized and that cognitively impaired individuals are not selected for research because of ease of recruitment or availability (p. 12).
 - The proposed setting for research should also be examined, if appropriate (p. 12).
 - IRBs should pay particular attention to the rationale behind enrolling vulnerable patients for research protocols that do not explicitly study medical conditions that impair consent capacity (p. 12).
- b. Where appropriate, an IRB should require that protocols include evidence of safety and efficacy from studies conducted with non-impaired individuals with consent capacity, particularly for research that does not offer a prospect of direct benefit and which has either a minor, or more than minor, increase over minimal risk (p. 12).
- c. An IRB should examine a study's proposed capacity assessment protocols to ensure that (p. 30-32):
 - the evaluation methods are appropriate for the research population;
 - any reassessments are undertaken in a timely manner; and
 - independent evaluators of capacity are used, where appropriate.
- d. An IRB should confirm that procedures are in place to maintain an appropriate level of care for individual participants, including personalized attention to ensure safety and the use of required medical and therapeutic procedures, where appropriate (p. 21).
- e. Where appropriate, an IRB should invite patients affected by relevant diseases that impair cognition, their family members, patient advocates, and knowledgeable experts to IRB meetings to provide additional guidance and insight on these research protocols (p. 13).
- f. An IRB should rigorously scrutinize a research protocol – especially those involving adults without consent capacity – for any potential or actual conflict presented by an institution, a researcher, and any other individual who is responsible for the design, operation, or reporting of the study (p. 14).
- g. An IRB should examine a protocol to ensure that the use of financial compensation is not an undue inducement to the participant or the LAR for participation (p. 15).
- h. An IRB should confirm that procedures are in place to allow for safe withdrawal from a study, where desired by the participant, LAR, or researcher (p. 37-38).
- i. For research not under federal purview, an IRB should prepare and maintain documentation of its activities and findings, comparable to those contemplated by federal regulations governing human subjects research. Such documentation may include evaluations of

capacity of participants, procedures used to identify LARs for surrogate consent to research, an overview of the risk-benefit analysis used, and a summary of various risk levels involved in approved protocols (p. 56).

- j. For any non-federal research protocol, IRBs should have methods for the identification, management, and reporting of adverse events and unanticipated problems that may occur during the course of a research protocol, comparable to those contemplated by the federal Common Rule (p. 56-57).
- k. IRBs should report to the Department of Health any violations of approved principles and policies which the IRB's institution has promulgated (p. 56-57).

2. Risk-Benefit Analysis

- a. With respect to benefits, an IRB should review (p. 15):
 - Whether same or similar benefits are available outside the context of research;
 - The intent of the researcher and purpose of the study;
 - The likelihood that all participants will receive the benefit; and
 - The extent or amount of the potential direct benefit.
- b. With respect to risk, an IRB should:
 - Verify that risks are minimized to the extent possible (p. 21); and
 - Review the type, probability, and degree of risk, including how the risks may disproportionately affect individuals lacking consent capacity, physically infirm persons, or those who are unable to express discomfort or communicate their wishes (p. 19).
- c. An IRB should review and approve studies that present a reasonable balance of potential benefits to risks (p. 21).
 - An IRB should examine the extent or amount of any claimed potential direct benefit in relation to any harmful side effects (p. 21).
- d. An IRB should analyze the risks and benefits as a whole of each proposed study (p. 21).
- e. An IRB may require a lower risk ceiling for allowable risk or a more favorable risk-benefit ratio for a study to be approved. However, for research that may offer a prospect of direct benefit, an IRB may allow a higher ceiling for allowable risk or a less favorable risk-benefit ratio for research (p. 22-23).
- f. An IRB should determine whether the research is of "vital importance," i.e., there is clear and significant evidence that the use of such a procedure or intervention presents a reasonable opportunity to further the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder (p. 23).
- g. An IRB may require additional safeguards, such as informed consent monitors (ICMs) or medically responsible clinicians (MRCs) as the risk level increases and/or the prospect of direct benefit diminishes to ensure the safety and well-being of participants (p. 24).
- h. If an ICM is used, the role and responsibilities of an ICM may vary and the degree of involvement would be determined by the IRB (p. 52).
- i. Both the degree of scrutiny by an IRB and the determination of the number and type of additional protections that may be required should be unique to each study, and should be calibrated according to the risk level and whether the study offers the prospect of direct benefit (p. 24).
- j. With respect to approving research protocols, IRBs should use the following approach to oversee risk-benefit ratios:

1. For research with minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies (p. 24):
 - if the risks are reasonable in relation to the prospective benefits.
2. For research with minimal risk and *no prospect of direct benefit* to the participant, IRBs may approve such studies (p. 24):
 - if the research is important to advance the scientific knowledge of a medical condition that affects the research population, *and*
 - if the risks are reasonable in relation to such importance.
3. For research with a minor increase over minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies only (p. 24):
 - if the risks are reasonable in relation to the prospective benefits, and
 - if the potential benefits are similar to those available in the standard clinical or treatment setting, *and*
 - if the risk-benefit ratio is favorable to participants.

IRBs may recommend the use of ICMs or may strongly recommend MRCs or other additional safeguards.
4. For research with a minor increase over minimal risk and *no prospect of direct benefit* to the participant, IRBs may approve such studies only (p. 24-25):
 - if the research is vitally important to further the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population, *and*
 - if the risks are reasonable in relation to the research's "vital importance."

Furthermore, IRBs may approve such studies only if they require mandatory rigorous procedures and oversight for enrollment and monitoring of participants through the use of safeguards, including an ICM and an MRC.
5. For research with more than minor increase over minimal risk and a *prospect of direct benefit* to the participant, IRBs may approve such studies only (p. 25):
 - if the risks are reasonable in relation to the prospective benefits, and
 - if the potential benefits are similar to those available in the standard clinical or treatment setting, *and*
 - if the risk-benefit ratio is favorable to participants.

IRBs should require additional safeguards, such as the use of ICMs and MRCs.
6. For research with more than minor increase over minimal risk and *no prospect of direct benefit* to the participant, IRBs may approve such studies under two circumstances (p. 25):
 - IRBs determine that: (a) all potential participants, when they still had capacity, have executed legally binding documents such as Research Advance Directives (RAD) which explicitly state that they are willing to participate in this category of research, (b) the research is of vital importance to the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population and/or those similarly situated, and (c) certain safeguards, such as an ICM and MRC, are in place, *or*
 - If potential participants do not have an RAD, a three step process involving the IRB and Department of Health may proceed in order for the protocol to be approved:
 - (1) The IRB must examine if:

- the research of is vital importance to the understanding of the etiology, prevention, diagnosis, pathophysiology, or alleviation or treatment of a condition or disorder that affects the research population and/or those similarly situated,
- that the risks are reasonable in relation to such vital importance, *and*
- mandatory rigorous procedures and oversight for enrollment and monitoring of participants through the use of safeguards, including an ICM and MRC, are in place.

(2) If the conditions in (1) are satisfied, the IRB should notify the Department of Health. At its discretion, the Department may: (a) reject the study and the research could not be approved by the IRB, (b) approve the study and the research could be approved by the IRB, *or* (c) convene a special review panel of experts which will review the study and issue recommendations to the IRB on whether the study should be approved.

(3) If the protocol has been referred to a special review panel, the IRB will make the final decision to approve or reject the study, with or without any modifications to the protocol.

- k. An IRB may determine that only specific classes of LARs may provide consent in certain research situations – especially where the research involves higher risk levels with no prospect of direct benefit. The riskier the research protocol and/or more remote the prospect of direct benefit, the closer the LAR (i.e., by kinship or intimacy level) should be to the potential participant (p. 43).

B. Responsibilities of Researchers

1. General Responsibilities

- a. Researchers should:
 - Utilize the least burdened population and provide justification for the use of these individuals and for the specific institutional settings, if appropriate (p. 12);
 - Provide evidence of safety and efficacy data from studies conducted in a non-impaired group prior to inclusion of cognitively impaired individuals, particularly for high risk or no-direct-benefit research, if appropriate (p. 12);
 - Minimize risks to participants (p. 21); and
 - Incorporate procedures to maintain participants' care, including personalized attention to ensure safety and the maintenance of required medical and therapeutic procedures, where appropriate (p. 21).
- b. Researchers conducting studies under Public Health Law 24-A involving individuals unable to provide consent should be subject to federally-mandated reporting requirements and should provide such documentation to the IRB (p. 56).
- c. Researchers should disclose relevant information to LARs and participants of how the study will be conducted and provide regular updates on the status of the participant and the progress of the study (p. 56).
- d. For any non-federal research protocol, researchers should have methods for the identification, management, and reporting of adverse events and unanticipated problems that

may occur during the course of a research protocol, comparable to those contemplated by the federal Common Rule (p. 56).

- e. Researchers should develop formal procedures to ensure that the withdrawal mechanisms are appropriate to the research population, that withdrawal is accomplished with the least risk to the participant when it is reasonable and safe to do so, that proper reporting practices to the IRB regarding the withdrawal, including the reason for it and whether the withdrawal was from all aspects of the research or only the primary interventional or procedural component, and who made the request for withdrawal, are in place (p. 37-38).
 - Researchers should honor all requests to withdrawal from research unless there are extraordinary circumstances concerning the participant's safety that would preclude immediate withdrawal (p. 37).

2. Capacity Assessments

- a. Researchers should explain why a particular screening tool is used and how it accounts for the degree of impaired consent capacity of the research population (p. 31).
- b. Researchers should develop procedures for the monitoring of participant's capacity through the course of the study, if appropriate (p. 31).
- c. Researchers should reassess capacity for individuals who exhibit fluctuating capacity levels and in other instances where reassessment is deemed appropriate (p. 31-32).
- d. Researchers should describe the qualifications of the person conducting the assessment and state whether the person is affiliated with the study and should consider the use of an independent evaluator of capacity (p. 33).
- e. Researchers should provide notice to the potential participant and/or LAR that an assessment will be conducted and the consequences (if any) of a determination of incapacity (p. 33).
- f. Researchers should state whether the results of the capacity assessment will be entered into the individual's medical record (p. 33).

3. Informed Consent

- a. Researchers should seek to obtain first-person informed consent from the research participant wherever possible and steps should be taken to ensure first-person decision-making, if possible. Consent should be re-obtained when circumstances significantly change the potential benefits or risks or harms, or when new scientific information becomes available (p. 34).
- b. When seeking to obtain informed consent from either the research participant or the LAR, researchers should:
 - Use a dynamic process to facilitate discussion and true understanding of the risks and benefits of participation (p. 34);
 - Present information using methods that are appropriate to the consent capacity of the research population and attempt to provide information in a variety of ways (p. 34);
 - Pay attention to information delivery and accessibility of information provided (p. 36);
 - Utilize a neutral discloser, wherever possible (p. 34 and 48). If a member of the research team or the individual's health care provider participates in the informed consent process, his/her role must be disclosed and additional care must be taken to ensure that information is provided in a transparent, accurate, and unbiased manner (p. 34);

- Seek re-consent, where appropriate (p. 32); and
- Make scrupulous efforts to ensure that potential participants and/or their LARs understand the difference between the goals of research and the goals of clinical care to help dispel the therapeutic misconception (p. 48).

4. Participant Assent

- a. If an individual is unable to provide first-person consent, researchers may not enroll an individual in research unless (p. 36):
 - An LAR provides informed consent (p. 38); *and*
 - The individual provides assent to participation, where capable, or does not dissent (p. 36).
- b. If the individual is unable to provide or express assent, researchers should provide an opportunity to express signs of dissent (recognizing that dissent may be expressed in different forms, depending on the individual's degree of impairment) (p. 36).
- c. If signs of dissent are present or – where assent is possible – there is an absence of assent, researchers may not enroll or allow continued participation of the individual in the study (p. 36).

5. Consent by LARs

- a. Researchers may limit which classes of LARs may provide surrogate consent, particularly for research that has no prospect of direct benefit and involves a minor increase over minimal risk, or more than a minor increase over minimal risk (p. 43).
- b. Researchers should give preference to an LAR selected by an individual, particularly where the selection was made when the individual had consent capacity and selected the individual using a legally binding document (i.e., health care proxy or RAD) over LARs appointed by statutory or regulatory mechanisms (p. 44).
- c. Researchers should scrutinize whether the LAR might be the true beneficiary of any financial compensation offered or the enrollment might alleviate the burdens of caring for the potential participant, to prevent undue inducement to consent to research (p. 49).

C. Responsibilities of LARs

- a. When considering a research protocol, an LAR should understand the distinction between research and treatment and examine (p. 46):
 - The potential risks and benefits of a research protocol;
 - The likelihood and extent the participant will receive any direct benefit or experience any adverse consequences/risk; and
 - Whether any potential benefits offered to the participant could be obtained in the treatment context.
- b. When determining whether an individual should participate in research, an LAR should use (p. 46-47):
 - Instructions from an RAD or similar type of advance directive, if such instructions exist;
 - or*
 - The participant's prior expressed wishes and preferences about research, if known; *or*

- If there are no prior expressed wishes, the LAR should use either the best interest standard or substituted judgment:
 - Application of the best interest standard should ensure respect for the individual and provide the most benefit to him/her. This standard may be most applicable to research that offers a prospect of direct benefit.
 - The substituted judgment standard must incorporate the values and beliefs of an individual that can be applied to the research context. This standard should generally be applied to research that does not offer a prospect of direct benefit.
- c. An LAR may not consider financial remuneration as a direct benefit (p. 49).
- d. An LAR should understand his/her role and responsibilities, be an advocate for the participant, and be available for any additional decision-making, where necessary (p. 47).
- e. A person shall not serve as an LAR where s/he has a conflict of interest or provide surrogate consent to research when s/he is an LAR for multiple cognitively-impaired individuals (p. 44).

D. Recommendations to the New York State Department of Health

- a. The Department of Health should be notified of all research protocols that involve more than a minor increase over minimal risk without a prospect of direct benefit that fall under state purview (p. 26). At the discretion of the Department of Health, the Department may (p. 26-27): (1) reject the study, (2) approve the study, or (3) convene a special review panel of experts who will examine the study and issue recommendations to the IRB on whether the study should be approved.
 - If the Department convenes a special review panel (p. 26-27):
 - Panelists should be comprised of relevant experts knowledgeable about the conditions(s) or population(s) addressed by the research;
 - Panelists should be required to provide a written report that will be publicly available and will include a summary of the panel's reasoning and analysis and recommendation to the IRB, who will either reject or approve the study, with or without any modifications to the protocol; and
 - The panelists' recommendations will be kept by the Department of Health and made available to the public upon request.
- b. The Department of Health should develop State Multiple Project Assurances (MPAs) with research entities and institutions to streamline protocol review for non-federally regulated research (p. 54).
 - The State MPA could obviate the need for full Commissioner/Department of Health review for research involving cognitively impaired individuals that involves minimal risk or a minor increase over minimal risk, with or without a prospect of direct benefit, and for research that involves more than a minor increase over minimal risk with a prospect of direct benefit. However, for research that involves more than a minor increase over minimal risk, *without* a prospect of direct benefit, a State MPA should not be a valid release from notification to the Department of Health and a special review panel may be convened, if necessary (p. 54 and p. 26-27).

Appendix A
Members of the Task Force on Life and the Law

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| <p>Nirav R. Shah, M.D., M.P.H. Commissioner of Health, New York State</p> <p>*Richard F. Daines, M.D. Former Commissioner of Health, New York State</p> <p>Karl P. Adler, M.D. Cardinal’s Delegate for Health Care, Archdiocese of NY</p> <p>*Adrienne Asch, Ph.D., M.S. Director, Center for Ethics at Yeshiva University</p> <p>Donald P. Berens, Jr., J.D. Former General Counsel, New York State Department of Health</p> <p>*Rev. Thomas Berg, Ph.D., M.A. Professor of Moral Theology, St. Joseph Seminary</p> <p>Rabbi J. David Bleich, Ph.D. Professor of Talmud, Yeshiva University Professor of Jewish Law and Ethics, Benjamin Cardozo School of Law</p> <p>*Kathleen M. Boozang, J.D. Associate Dean for Academic Advancement Seton Hall University School of Law</p> <p>Rock Brynner, Ph.D., M.A. Professor and Author</p> <p>Karen A. Butler, R.N., J.D. Partner, Thuillez, Ford, Gold, Butler & Young, LLP</p> <p>Carolyn Corcoran, J.D. Principal, James P. Corcoran, LLC</p> <p>*Lyla Correoso, M.D. National Hospice Medical Director, Gentiva Hospice</p> <p>Nancy Neveloff Dubler, LL.B. Consultant for Ethics, NYC Health & Hospitals Corp. Professor Emerita, Albert Einstein College of Medicine</p> <p>Paul J. Edelson, M.D. Adjunct Professor of Clinical Pediatrics, College of Physicians and Surgeons, Columbia University</p> <p>Joseph J. Fins, M.D., M.A.C.P. Chief, Division of Medical Ethics, Weill Medical College of Cornell University</p> <p>*Alan R. Fleischman, M.D. Clinical Professor, Albert Einstein College of Medicine</p> | <p>Rev. Francis H. Geer, M.Div. Rector, St. Philip’s Church in the Highlands</p> <p>*Jane Greenlaw, R.N., J.D. Professor Emerita University of Rochester School of Medicine and Dentistry</p> <p>Samuel Gorovitz, Ph.D. Professor of Philosophy, Syracuse University</p> <p>Cassandra E. Henderson, M.D., C.D.E., F.A.C.O.G. Director of Maternal Fetal Medicine Lincoln Medical and Mental Health Center</p> <p>Hassan Khouli, M.D., F.C.C.P. Chief, Critical Care Section, St. Luke’s – Roosevelt Hospital</p> <p>Rev. H. Hugh Maynard-Reid, D.Min., B.C.C., C.A.S.A.C. Director, Pastoral Care, North Brooklyn Health Network, New York City Health and Hospitals Corporation</p> <p>*Kathryn C. Meyer, J.D. Evp Chief Legal Officer Beth Israel Medical Center</p> <p>John D. Murnane, J.D. Partner, Fitzpatrick, Cella, Harper & Scinto</p> <p>Samuel Packer, M.D. Chair of Ethics, North Shore-LIJ Health System</p> <p>*Rabbi A. James Rudin, D.D. Senior Interreligious Advisor American Jewish Committee</p> <p>*Barbara Shack Health Policy Consultant</p> <p>*Daniel P. Sulmasy, O.F.M., M.D., Ph.D. Associate Director, The MacLean Center University of Chicago Medical Center</p> <p>Robert Swidler, J.D. VP, Legal Services St. Peter’s Health Partners</p> <p>Sally T. True, J.D. Partner, True and Walsh, LLP</p> <p>*Rogelio Thomas, M.D., M.P.P. President, Special Care Medical Associates, PC</p> <p>* Indicates former member</p> |
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Task Force on Life and the Law Staff

| | |
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| <p>Susie A. Han, M.A., M.A. Deputy Director, Principal Policy Analyst</p> <p>Valerie Gutmann Koch, J.D. Senior Attorney</p> <p>*Carrie S. Zoubul, J.D., M.A. Former Senior Attorney</p> <p>Stuart Sherman, J.D., M.P.H. Executive Director</p> <p>Angela R. Star Administrative Assistant</p> | <p>*Beth E. Roxland, J.D., M.Bioethics Former Executive Director</p> <p>*Tia Powell, M.D. Former Executive Director</p> <p>*Kelly Christ Pike, M.H.S. Former Principal Policy Analyst</p> <p>*Leah Kalm-Freeman, Ph.D. Former Principal Policy Analyst</p> <p>* Indicates former staff member</p> |
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Department of Health Liaison

| | |
|--|--|
| <p>James Dering, J.D. General Counsel New York State Department of Health</p> | <p>*Tom Conway, J.D. Former General Counsel New York State Department of Health</p> <p>* Indicates former staff member</p> |
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Appendix B
Task Force’s Recommendations Regarding Additional Safeguards
Based on Risk-Benefit Categories

ICM = Independent Consent Monitor
MRC = Medically Responsible Clinician
MPA = Multiple Project Assurance

| | Minimal Risk | Minor Increase Over Minimal Risk | More Than a Minor Increase Over Minimal Risk |
|--------------------------------------|------------------------|----------------------------------|--|
| Prospect of Direct Benefit | ICM – Usually Optional | ICM – May Recommend | ICM – Require |
| | MRC – Optional | MRC – Strongly Recommend | MRC – Require |
| | MPA – Support | MPA – Support | MPA – Support |
| No Prospect of Direct Benefit | ICM – Usually Optional | ICM – Require | ICM – Require |
| | MRC – Optional | MRC – Require | MRC – Require |
| | MPA – Support | MPA – Support | MPA – Insufficient, DOH review required |