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"Of Vital Importance": The New York State Task Force on Life and the Law's Report and Recommendations for Research with Human Subjects Who Lack Consent Capacity (with Susie A. Han)

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"Of Vital Importance": The New York State Task Force on Life and the Law's *Report and Recommendations for Research with Human Subjects Who Lack Consent Capacity*

By Valerie Gutmann Koch and Susie A. Han

American history has been rife with human subjects research (HSR) scandals—particularly those that involve "vulnerable" populations—including several in New York State, such as those that occurred at the Willowbrook State School and the Jewish Chronic Disease Hospital.[1] In response, state and federal laws and regulations were enacted to ensure voluntary informed consent for participants and institutional review board (IRB) oversight of HSR. However, these laws and regulations do not provide any special oversight mechanisms or protections to ensure the ethical and safe inclusion of cognitively impaired adults in research.

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, 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—if any—rules and little guidance at both the federal and state level to ensure consistently ethical conduct of research involving adults lacking consent capacity. While some institutions and investigators are conducting researching with this population without oversight or guidance, others are taking an extremely conservative approach and are excluding these individuals from research, citing concerns about vulnerability and exploitation. Without safeguards that are both adequate and robust but not overly burdensome, this will remain a challenge to the conduct of ethical research. Thus, IRBs, investigators, and research institutions have appealed to the New York State Task Force on Life and the Law (the Task Force)[2] for guidance on how to conduct research involving this vulnerable population.

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. Laws that exclude individuals who lack consent capacity actually disadvantage this population by preventing scientific advances for conditions that cause decisional incapacity. Although concerns about how to conduct research involving individuals unable to give first-person informed consent are valid and important, justice requires the creation of guidance and procedures that will allow these individuals to benefit from scientific advances while ensuring that their interests are protected.

To address this significant inconsistency in the oversight and conduct of research, the Task Force drafted a set of legal and ethical guidance regarding the conduct of research in New York State involving adults who lack consent capacity. This article addresses the development and key content of the guidance, which may serve as a model for research in other states and at the federal level. An underlying goal of the 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, the report provides guidance and best practices that will assist institutions, researchers, IRBs, and surrogate decision-makers in the ethical conduct and responsibilities of research involving the cognitively impaired. Without such guidance, either research will occur without appropriate protections and safeguards, or important research may not occur.

Methods

At the request of various stakeholders, the Task Force analyzed the legal and ethical implications of research involving adults lacking consent capacity. The Task Force began this endeavor 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. 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.

Since 2007, the Task Force has devoted itself to examining the issues associated with research involving cognitively impaired adults. It reviewed medical and policy literature on human subjects research, informed consent, surrogate consent, capacity assessment, risk-benefit analysis, research protections, adverse events, 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. It reached out and relied on

testimony from several experts from research institutions, governmental entities, and patient advocacy organizations. The Task Force analyzed previously released reports, recommendations, and draft regulations on human subjects research by the Department of Health and the public comments to these efforts,[3] and stakeholders and other interested parties provided additional perspectives and input on this project. It also took into account the controversial advisory opinion in the case *T.D. v. N.Y. State Office of Mental Health*,[4] in which the court addressed the need for special protections where research includes individuals who lack consent capacity when surrogate consent is used.

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,[5] no statutory change is needed. The Task Force therefore identified approaches that comply with current federal and state law, including the Common Rule and New York Public Health Law 24-A,[6] to ensure ethical practices in research involving this vulnerable population.

Recommendations

In order to promote a consistently ethical approach by institutions to the protection of this vulnerable population in New York State, the Task Force made a number of important and—in some cases—unique recommendations regarding including individuals who lack consent capacity in human subjects research.[7] This guidance is necessary in order to ensure that this population is able to participate in research (as the law anticipates) with adequate and appropriate safeguards in place.

A. Participant Selection

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 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,[8] because research involving these groups may be seen as increasing the risks and potential harms for an already burdened population.[9]

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.

B. Benefits and Risks

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.

One of the core functions of an IRB is to review and approve studies that present a reasonable balance of potential benefits to risks. Research protocols can be classified as either *prospect-of-direct-benefit* or *no-direct-benefit* studies, 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. No-direct-benefit studies have a negligible or nonexistent probability of offering a benefit to participants.

One of the most complex ethical issues in conducting research involving these individuals is the degree of risk to which researchers may ethically expose this population. While upper limits on the level of acceptable risk may be necessary for some HSR studies, bright-line cut-offs are only appropriate in limited circumstances. The Task Force recommends that 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.

In 1977, the National Commission issued a report on research involving children, suggesting a tripartite scheme for classifying research risks.[10] 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[11] and has

been used in numerous expert commission reports and state regulations delineating research risk in all human subjects research.[12] Although the tripartite risk scheme presents difficulties in application, it remains the most recognized and most used method to classify risks levels. The Task Force concluded that these three major risk levels are appropriate for IRBs and researchers to use for research involving individuals who lack consent capacity.

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.

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. However, for research that may offer a prospect of direct benefit, 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; clarity (or its absence) often depends on the current state of available scientific knowledge. 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.[13] The IRB should carefully review the hypotheses of the study and antecedent evidence, such as data from animal studies, analogous research,[14] 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. Furthermore, the IRB should also examine the researchers' therapeutic intent[15] and the purpose of the research study to determine whether the research is of vital importance and should be approved.

The Task Force recommends that it is acceptable for IRBs to require additional safeguards (such as requiring or recommending informed consent monitors (ICMs) and medically responsible clinicians (MRCs)) to ensure the safety and well-being of vulnerable participants. 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, IRBs may approve such studies only 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."[16] 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 only two circumscribed circumstances: where the potential participants have a research advance directive *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), which provide an individual's instructions for future research participation should s/he lose consent capacity, that 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 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

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, and thus there are limited circumstances where a research protocol may be considered for approval even where potential participants do not have RADs. The Task Force therefore 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.[17] 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 experts[18] who will examine the study and issue 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.

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.[19] 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, 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 the general public to maintain confidence in the oversight process of this category of unique research.

C. Consent and Capacity Assessments

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, where possible, 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. The information should be presented using methods that are best suited to the capacity level of the target population. 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 Task Force recommends that informed consent be obtained, with the use of a neutral discloser, 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.

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 in a research study 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.[20]

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. Researchers should recognize that for this population, dissent may not be obvious. Furthermore, if signs of dissent are present, the researcher may not enroll or allow continued participation of the individual in the study.

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.

Consent capacity may be impaired due to medical conditions or illnesses, chronic diseases, medication, or developmental cognitive impairment.[21] 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.[22] Consent capacity has a complicated relationship to clinical diagnosis and is likely to fluctuate over time and may be task-specific. 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. Thus, the threshold that distinguishes individuals who meet the consent capacity standard varies between research protocols.

Current practices for screening and evaluating consent capacity vary in type[23] and quality.[24] 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 may be most useful. 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.

D. Legally Authorized Representatives

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 RAD. However, neither the federal nor state governments have directly addressed who should act as a research legally authorized representative (LAR) for the cognitively impaired.[25] If the legislature or Department of Health promulgates rules in the future regarding who may consent, different considerations and standards of decision-making should apply to research than to treatment.[26]

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 RAD. 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.[27] 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.[28] The Task Force also recommends the placement of restrictions on who may serve as an LAR to ensure that participants are adequately protected.[29]

Where an RAD has not been previously executed, it may be permissible, in some cases, for individuals lacking consent capacity to be enrolled in a research protocol with the consent of an LAR. Federal law clearly contemplates allowing surrogates to consent to research involving adults who lack consent capacity.[30] An LAR is defined under the Common Rule 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…."[31] However, federal law defers to the states to establish who may serve as an LAR, looking to their formulations of LAR to determine who may consent to research conducted in that state. Because New York's laws for human subjects research do not provide a research-related LAR hierarchy, the 2010 passage of the Family Health Care Decisions Act (FHCDA) changed the legal landscape by permitting surrogate consent to health care.[32] The surrogate hierarchy contained in the FHCDA thus opened up the field of research requiring surrogate consent in New York State.

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. 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. 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.[33]

When determining whether an individual should participate in research, an LAR should use 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. If there are no prior expressed wishes, the LAR should use either the best interest standard or substituted judgment.

Finally, to prevent undue inducement to consent to research, LARs may never be the true beneficiary of any financial compensation offered.

E. Notice to Participant and Opportunity for Review

The Task Force emphasized the importance of procedures for providing notice to the potential research participant and, if necessary, the LAR, regarding the capacity assessment and opportunities for objection and review. 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.

As part of a research protocol, the Task Force recommends that potential participants and/or LARs should be notified of a planned capacity assessment, as well as the results of the assessment and any consequences of a determination of incapacity. Providing notice promotes transparency by alleviating any concerns that an individual might be involved in research without the knowledge of the participant or LAR. It also demonstrates respect for the prospective participant by presenting an opportunity for the individual or his/her LAR 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 LARs 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.

F. 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. The amount and scope of additional safeguards that the Task Force recommends for research with this population depends on the level of risk and the likelihood of direct benefit that the research protocol offers to the research 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.

1. Independent Consent Monitors (ICMs)

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 process[34]—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.[35] 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.[36]

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 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 study.[37] 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.[38]

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.

2. Medically Responsible Clinicians (MRCs)

Depending on the research study and risk level involved, use of an 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 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.[39] Thus, use of an MRC is an important safeguard for high risk studies because the physician acts as an 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.

3. Multiple Project Assurances (MPAs)

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.[40] However, to streamline the review process, the Task Force recommends that the Department of Health should develop MPAs[41] 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.

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.

4. Reporting Requirements

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.[42] 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; and a summary of various risk levels involved in approved protocols. 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.[43]

The Task Force recommends that researchers conducting studies under New York State's law governing HSR that involve 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.[44] In addition, the Task Force recommends that researchers should 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 under way, 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.

The disclosure of adverse events[45] and unanticipated problems[46] that result from research participation promotes transparency and may further protect the welfare of research participants.[47] The Office of Human Research Protections (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. 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.[48]

Conclusions

The Task Force's *Report and Recommendations for Research with Human Subjects Who Lack Consent Capacity* are the result of a multi-year effort to respond to appeals for guidance from New York State IRBs, investigators, and research institutions on how to conduct ethical research involving adults who lack consent capacity. Although New York State law governs human subjects research for a subset of research conducted in the state by providing mechanisms for ensuring voluntary informed consent for participants and IRB review of research protocols, it does *not* provide any special oversight mechanisms for research involving this particular population. Despite calls to do so, federal law also does not provide safeguards or special protections for research involving "mentally disabled persons."[49] The absence of such guidelines or regulations may lead to unethical or unsafe research protocols or the dearth of important research into the broad range of diseases that impair cognition.

Thus, an underlying goal of the Task Force's work is to ensure that research protocols are available to all

individuals, including individuals who lack consent capacity, so that they may also experience the benefits, risks, and burdens of research as their non-cognitively impaired peers, while also ensuring the appropriate level of protections. Although the guidelines focus only on the inclusion of these individuals in research in New York State, the recommendations could serve as a model for the development of other policies in other states and at the federal level.

For more information regarding the Task Force's analysis and recommendations, as well as more on the legal implications of research involving adults lacking consent capacity, see the Task Force's full report, *Report and Recommendations for Research with Human Subjects Who Lack Consent Capacity*, at: http://www.health.ny.gov/regulations/task_force/reports_publications/.

Endnotes

1. H.K. Beecher, *Ethics and Clinical Research, New England Journal of Medicine*, 274, no. 24 (1966): 1354-60.
2. 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* http://www.health.ny.gov/regulations/task_force/ for the list of past and current Task Force projects and current members.
3. 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, accessed 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).
4. The New York State Office of Mental Health promulgated regulations in 1990 governing research with adults lacking consent capacity, but they were struck down because only the Commissioner of Health has the authority to promulgate regulations under Article 24-A. 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).
5. N.Y. Pub. Health Law §§ 2440–2442; Subpart A of 45 C.F.R 46 (The Common Rule). 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.
6. Article 24-A applies to human subjects research conducted in New York state 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." 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 United States Department of Health and Human Services a "multiple project assurance," voluntarily agreeing to comply with federal human subjects research regulations. See *T.D.*, 228 A.D.2d 95.
7. For more information, particularly regarding the justifications for the Task Force's recommendations and the legal implications of research involving adults lacking consent capacity, see the Task Force's full report, *Report and Recommendations for Research with Human Subjects Who Lack Consent Capacity*.
8. 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.
9. 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 may therefore be subject to real or perceived coercion by staff to participate.
10. 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.
11. 45 C.F.R. §§ 46.103, 46.109, 46.116-17, 46.405.
12. 45 C.F.R. § 46 (Subpart D); "1998 New York State Work Group Report," *supra* note 3, at 14; Office of the Maryland Attorney General, "Final Report of the Maryland Attorney General's Research Working Group," 1998, at A-17 [hereinafter "Maryland Attorney General Report"].
13. Office for Human Research Protections, "Secretary's Advisory Committee on Human Research Protections (SACHRP), Appendix B," http://www.hhs.gov/ohrp/sachrp/sachrpltrtohhssecapdb.html, accessed April 16, 2013.
14. In the context of the 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.
15. It may be prudent to separate therapeutic *intent* from therapeutic *benefit*, especially when the extent of potential benefit has not been established. *See* J.J. Fins, "A Proposed Ethical Framework for Interventional Cognitive Neuroscience: A Consideration of Deep Brain Stimulation in Impaired Consciousness," *Neurological Research* 22, no. 3 (2000): 273-78, at 274-275. 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.
16. 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).
17. *See* Fins, "A Proposed Ethical Framework for Interventional Cognitive Neuroscience," 274-275.
18. One model for such a review panel is the federal 407 Review Children's Panels under the Common Rule, which examines research protocols involving children that are otherwise not approvable because of their risk level. *See* 45 C.F.R. § 46.407.
19. 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.
20. 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 the past, there has been 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.

21. 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.

22. S.Y. Kim et al., "Assessing the Competence of Persons with Alzheimer's Disease in Providing Informed Consent for Participation in Research," *American Journal of Psychiatry* 158, no. 5 (2001): 712-17, at 716; C.B. Fisher et al., "Capacity of Persons with Mental Retardation to Consent to Participate in Randomized Clinical Trials," *American Journal of Psychiatry* 163, no. 10 (2006): 1813-20, at 1818-19; V.D. Buckles et al., "Understanding of Informed Consent by Demented Individuals," *Neurology* 61, no. 12 (2003): 1662-66, at 1665.

23. 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. E.D. Sturman, "The Capacity to Consent to Treatment and Research: A Review of Standardized Assessment Tools," *Clinical Psychology Review* 25, no. 7 (2005): 954-74, at 964. 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. L.B. Dunn et al., "Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments," *American Journal of Psychiatry* 163, No. 8 (2006): 1323-34, at 1331; J.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," *Journal of the American Geriatrics Society*, 50, no. 12 (2002): 2019-24, at 2023; D.V. Jeste et al., "A New Brief Instrument for Assessing Decisional Capacity for Clinical Research," *Archives of General Psychiatry* 64, no. 8 (2007): 966-74, at 968.

24. S.Y. Kim et al., "Variability of Judgments of Capacity: Experience of Capacity Evaluators in a Study of Research Consent Capacity," *Psychosomatics* 52, no. 4 (2011): 346-53, at 351-52 (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).

25. 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."

    45 C.F.R. § 46.102 (emphasis added). Thus, 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 ensconced in statute, regulation, case law, or other legally binding authority. The Office of Human Research Protections (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, accessed visited July 16, 2012. 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 (such as where the individual has executed an RAD).

26. *See, e.g.*, M.N. Gong et al., "Surrogate Consent for Research Involving Adults with Impaired Decision Making: Survey of Institutional Review Board Practices," *Critical Care Medicine*, 38, no. 11 (2010): 2146-54, at 2153.

27. S.Y. Kim, "The Ethics of Informed Consent in Alzheimer Disease Research," *Nature Reviews Neurology* 7, no. 7 (2011): 410-14, at 412 (noting that a significant number of Alzheimer's disease patients may be able to appoint an LAR in a "concurrent" rather than advance directive).

28. Such procedures may include a witness(es) and documentation for the appointment. *See* S.Y. Kim, "Preservation of the Capacity to Appoint a Proxy Decision Maker: Implications for Dementia Research," *Archives of General Psychiatry* 68, no. 2 (2011): 214-20, at 215-16 (discussing appointment of a proxy where a person does not retain sufficient enough capacity to consent to the protocol itself).

29. 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.

30. 45 C.F.R. § 46.112; 21 C.F.R. § 56.112.

31. 45 C.F.R. § 46.102.

32. N.Y. Pub. Health Law Art. § 29-cc (2010).

33. 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.

34. *See* Nat'l Bioethics Advisory Comm'n, "Research involving Persons with Mental Disorders that may Affect Decisionmaking Capacity Report and Recommendations," Vol. I. (1998): 21 (hereinafter "NBAC Report"); National Institutes of Health, Trans-NIH Bioethics Committee Working Group, "Research Involving Individuals with Questionable Capacity to Consent: NIH Points to Consider" (2009): 9, http://grants1.nih.gov/grants/policy/questionablecapacity.htm; "Maryland Attorney General Report," *supra* note 12, at A-5; D.L. Rosenstein & F.G. Miller, "Ethical Considerations in Psychopharmacological Research involving Decisionally Impaired Subjects," *Psychopharmacology* 171, no. 1 (2003): 92-97, at 94; Committee on Assessing the System for Protecting Human Research Participants, Institute of Medicine, "Responsible Research: A Systems Approach to Protecting Research Participants," Washington, DC (Daniel Federman et al., eds., The National Academies Press, 2002): 164.

35. NBAC Report, *supra* note 34, at 21.

36. "1998 New York State Work Group Report," *supra* note 3, at 22; H.J. Silverman et al., "European Union Directive and the Protection of Incapacitated Subjects in Research: An Ethical Analysis," *Intensive Care Medicine*, 30, no. 9 (2004): 1723-29, at 1727.

37. E.H. Morreim, "By Any Other Name: The Many Iterations of 'Patient Advocate' in Clinical Research," *IRB: Ethics & Human Research*, 26, no. 6 (2004): 1-8, at 5. 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 PRIM&R 2008 (Nov. 18, 2008).

38. 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. Ideally, an ICM would have experience serving as a surrogate decision-maker for a person who has had a similar disorder affecting consent capacity. J.F. & F.G. Miller, "Enrolling Decisionally Incapacitated Subjects in Neuropsychiatric Research," *CNS Spectrums* 5, no. 10 (2000): 32-40 (proposing a matrix of individuals and perspectives, which would assist with enrollment decisions).

39. "1998 New York State Work Group Report," *supra* note 3, at 21.

40. N.Y. Pub. Health Law § 2444.

41. 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.

42. 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.

43. N.Y. Pub. Health Law § 2444(2).

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

45. 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* Health and Human Services (HHS), "Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting to IRBs–Improving Human Subject Protection" (Jan. 2009), http: / / www.fda.gov / downloads / RegulatoryInformation / Guidances / UCM126572.pdf.

46. 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).

47. As with many of the topics discussed in the 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 for all research involving human subjects.

48. 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 Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events," (2007) http: / / www.hhs.gov / ohrp / policy / adverntguid.html. N.Y. Pub. Health Law Art. 24-A does not require such reporting.

49. 45 C.F.R. § 46.111.

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