THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON. D.C. 20201

JAN 16 2001

Dr. Harold Shapiro, Chair
National Bioethics Advisory Commission
6705 Rockledge Drive, Suite 700 MSC 7979
Bethesda, Maryland 20892-7979

Dear Dr. Shapiro:

I am pleased to forward to you a copy of the response of the Department of Health and Human Services (DHHS) to the National Bioethics Advisory Commission's report, *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. This* response is the product of a DHHS working group. consisting of representatives from all the relevant agencies within the Department, that was convened to review and address the specific recommendations of the NBAC report. The decisionmaking capacity report is a valuable document that not only contributes to the public discourse on the protection of vulnerable subjects in research but also provides important insights that will help the Department strengthen its policies and procedures for safeguarding the rights and welfare of such individuals.

With respect to NBAC's report on *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance,* another working group within the Department is reviewing the report and formulating a set of responses to its recommendations. We anticipate that a report will be forthcoming within the next few months.

I want to take this opportunity to extend my best wishes to you and the other. Commissioners and express my appreciation for the fine work that all of you have done and will continue to do.

Sincerely,

Donna E. Shalala

Enclosure

ANALYSIS AND PROPOSED ACTIONS REGARDING THE NBAC REPORT:

RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

Prepared by

HHS Working Group on the NBAC Report

EXECUTIVE SUMMARY

This document presents the findings and proposals of a multi-agency Working Group (WG) convened by the Office of Science Policy, Office of the Assistant Secretary for Planning and Evaluation to develop a proposed response by the Department of Health and Human Services (HHS) to the National Bioethics Advisory Commission (NBAC) Report entitled *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity* (the "Report"). The Report makes 21 recommendations, which are variously directed to investigators or institutional review boards (IRBs); the National Institutes of Health (NIH) or other HHS agencies and offices; other Federal agencies that, along with HHS, have adopted the Common Rule[*]; State legislatures; health professionals; or others responsible for human subject protections.

The WG commends NBAC for its thoughtful and insightful report. The WG agrees that, despite significant improvement in human subject protection during recent decades, difficult issues related to the participation in research of individuals with impaired decisionmaking capacity need further consideration. NBAC has performed a valuable service in bringing these matters to the Nation's attention.

The WG believes, with NBAC, that our goals must be "providing protection for persons with mental disorders while allowing important research to go forward." (Report at 41). This position is in harmony with *Mental Health: Report of the Surgeon General,* which emphasizes the "importance of a solid research base for every mental health and mental illness intervention" because "establishing mental health policy on the basis of good intentions alone can make bad situations worse; [whereas] evaluating the practicality and effectiveness of new approaches is efficient and, more critically, is accountable to those for whom an intervention is intended."[**] The WG agrees with many of NBAC's concerns and recommendations and has developed proposals for how HHS might appropriately respond to the Report.

In addition, the WG recognizes that NBAC currently is conducting a review of the entire system of human subject protections and that, upon completing this comprehensive review, may make additional recommendations affecting human research subjects with impaired decisionmaking capacity. The WG was mindful of that possibility in developing its proposals.

SCOPE OF APPLICABILITY OF NBAC'S RECOMMENDATIONS

The WG found some ambiguity as to who is to be protected by the Report's 21 recommendations. Certain NBAC recommendations refer to "persons [or subjects] with mental disorders that may affect decisionmaking capacity" (e.g., Recommendations 2 and 20), while others refer to "persons with mental disorders" (e.g., Recommendations 1, 3, and 18). Based upon an analysis of the entire Report, the WG interprets the intended scope of NBAC's recommendations to be "persons with mental disorders that may affect decisionmaking capacity," as listed in the title.

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[*] Most federal agencies that conduct or support research involving human subjects have adopted regulations based on the language set forth in Subpart A of 45 CFR 46. This set of common regulations is referred to as the Federal Policy (Common Rule) for the Protection of Human Subjects. The FDA regulations at 21 CFR Parts 50 & 56 are FDA's equivalent to the Common Rule.

[**] Mental Health Report, Executive Summary p. viii.

The WG agrees with NBAC that current procedures for human subject protection should be improved to adequately protect research participants whose decisionmaking ability is impaired because of a mental disorder. Because of the need to rely on surrogate decision-makers and concerns about a subject's susceptibility to undue influence and coercion, a subject who has impaired decisionmaknng capacity due to a mental condition may not be adequately protected by the current informed consent procedures.

However, the WG notes that some physical disorders or conditions also may result in impaired capacity to make decisions and therefore the ability to give voluntary informed consent to research. Either mental or physical conditions that impair decisionmaking capacity may make subjects vulnerable to coercion or undue influence and thus in need of protection. As NBAC observed, "many of the issues and concerns raised in this report (and, indeed, many of its recommended protections) could be applied to all persons with questionable or diminished capacity." (Report at p. 5).

Further, the WG is concerned that limiting the scope of protections may be perceived to be stigmatizing. Approximately one in five Americans experiences a mental disorder during the course of a year,[***] yet the preponderance are capable of making major life decisions. The WG agrees, and NBAC's Report takes pains to. emphasize, that a person is not decisionally incapacitated to consent to research merely because that Person has a mental disorder or mental illness. However, the Report's focus was not expressly extended beyond persons with mental disorders and that in itself may appear stigmatizing or could lead to inadvertent stigmatization in practice.

> **The WG therefore concludes that the scope of the Report's recommendations seem appropriately applicable to all persons with decisional impairment, irrespective of diagnosis.**

REGULATORY FRAMEWORK ENVISIONED BY NBAC

Four of NBAC's recommendations work in concert to call for a new regulatory framework:

> *Recommendation 2: Creation of a Special Standing Panel (SSP)*
>
> *Recommendation 10: Research Protocols Involving Minimal Risk*
>
> *Recommendation 11: Research Protocols Involving Greater than Minimal Risk that Offer the Prospect of Direct Medical Benefit to Subjects*
>
> *Recommendation 12: Research Protocols Involving Greater than Minimal Risk that Do Not Offer the Prospect of Direct Medical Benefit to Subjects*

The recommended framework would require IRBs to classify all proposed research involving persons with mental disorders that may affect decisionmaking capacity into one of the three categories specified by Recommendations 10-12. The current regulations do not require a classification of risk.

Further, if the proposed research does not offer the prospect of direct medical benefit and involves any

[***] Mental Health Report, Executive Summary, p. xii.

degree of risk greater than minimal risk, the subject could not be enrolled in the research by a legally authorized representative (LAR), except under one of two sets of circumstances. In addition to IRB approval, either (1) the subject must have executed an advance directive to participate in that type of research or (2) the research must be reviewed by a "Special Standing Panel" (SSP) convened by the Secretary and that panel must conclude that the protocol "offers the possibility of substantial benefit to the population under study, that its risks to subjects are reasonable in relation to this possible benefit, and that it could not be conducted without the proposed population," and the panel must be "satisfied that all appropriate safeguards are incorporated." If the SSP subsequently were to promulgate guidelines covering certain instances of that type of protocol, then only IRB approval and surrogate consent would be required unless the guidelines were to require more.

The WG agrees with the principle, reflected in NBAC's Recommendations 10, 11, and 12, that additional safeguards are warranted when research is directed toward subjects with mental or physical conditions that are associated with decisional impairment This principle is consistent with current requirements. However, the WG believes that widespread execution of Prospective Authorizations for research is unlikely and thus that the large number of proposed protocols that would require review by the SSP could make the envisioned regulatory framework impractical to implement Further, the WG notes that the envisioned regulatory framework would alter IRB authority in ways that could produce anomaloiis results. For example, under certain circumstances, NBAC's recommendations not only would limit IRB authority more for adults than for children but also would narrow the types of benefits that an IRB may consider in determining whether a greater than minimal risk protocol offers a direct benefit.

> **With regard to Recommendations 2, 10, 11, and 12, the WG proposes that the Office for Human Research Protections (OHRP), working in consultation with Food and Drug Administration (FDA), solicit additional public comment regarding appropriate approval standards as a function of differing levels of risk in research directed toward subjects with mental or physical conditions that are associated with decisional impairment. The WG proposes in particular that a formal Federal Register solicitation request comment on (i) appropriate mechanisms for ensuring needed protections; (ii) appropriate regulatory frameworks for characterizing informed consent and IRB approval requirements as a function of differing levels of risk; and (iii) acceptability of certain overarching principles.**

See "Discussion" and "Proposed Action" following Recommendation 12 for pertinent details regarding the form and content of the proposed solicitation of public comment.

RECOMMENDED PROTECTIONS INHERENT IN CURRENT REGULATIONS BUT POSSIBLY WARRANTING ADDITIONAL GUIDANCE

Eight of NBAC's recommendations are consistent with but generally more specific than the current regulations:

Recommendation 1: Institutional Review Board Membership

Recommendation 3: Appropriate Subject Selection

Recommendation 4: Justifying Research Designs and Minimizing Risks

Recommendation 5: Evaluating Risks and Benefits

Recommendation 7: Objection to Participation in Research

Recommendation 8: Assessing Potential Subjects' Capacity to Decide about Participating in a Research Protocol

Recommendation 9: Notifying Subjects of Incapacity Determinations and Research Enrollment

Recommendation 17: Involving Subjects' Family and Friends

The WG agrees in principle regarding all eight recommendations, but for five of them (1, 4, 8, 9, and 17) it offers an alternative perspective on certain facets for consideration by OHRP and FDA.

The WG proposes that, after consideration of this Analysis and consultation with FDA, OHRP develop and issue additional interpretive guidance in response to Recommendations 1 and 3.

The WG proposes that, after consideration of this Analysis and consultation with FDA, OHRP take whatever actions it deems appropriate regarding Recommendations 4, 5, 7, 8, 9, and 17.

ADDITIONAL RESEARCH RELATED TO DECISIONAL IMPAIRMENT

Two of NBAC's recommendations are related to additional research related to decisional impairment:

Recommendation 19: Expanding Knowledge about Capacity Assessment and Informed Consent

Recommendation 20: Institute of Medicine Review of Research Studies

Recommendation 19 is addressed explicitly to the NIH. For recommendation 20, the NIH is the appropriate lead agency for HHS.

The WG proposes that the Director, NIH determine and take whatever action is needed in regard to Recommendations 19 and 20.

STATE LAWS RELATED TO RESEARCH INVOLVING PERSONS WHOSE DECISIONMAKING CAPACITY MAY BE IMPAIRED

Four of NBAC's recommendations address legal matters that fall substantially, if not entirely, within the province of States:

Recommendation 13: Prospective Authorization

Recommendation 14: Legally Authorized Representatives

Recommendation 15: Expansion of the Category of Legally Authorized Representatives and of the Powers Granted under Statutes for Durable Powers of Attorney (DPA) for Health Care

Recommendation 16: State Legislation Regarding Advanced Directives for Research

The WG recognizes that the options of the federal government in these areas are heavily dependent upon what actions, if any, States take.

The WG proposes' that the Secretary make the States aware of NBAC's Recommendations 13-16 and our proposed actions and encourage the States to consider them, by sending copies of NBAC's Report and this Analysis to the States' Attorneys General.

OTHER TOPICS

Recommendation 6: Informed Consent

Recommendation 18: Reviewing and Developing Educational Materials Regarding Research

Recommendation 21: Increased Funding to Support Necessary Protections of Human Subjects)

Recommendation 6 requires no action. Recommendation 18 is directed to professional associations and organizations. Recommendation 21 is directed to all research sponsors, including HHS.

With regard to Recommendation 21, the WG proposes that HHS continue its efforts to increase the financial support available to IRBs.

ANALYSIS AND PROPOSED ACTIONS REGARDING THE NBAC REPORT:
RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

INTRODUCTION

The National Bioethics Advisory Commission (NBAC) presented its report entitled *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity* (the "Report") to the National Science and Technology Council (NSTC) in January, 1999. The Report makes 2I recommendations, which are variously directed to investigators or institutional review boards (IRBs); the National Institutes of Health (NIH) or other agencies and offices of the Department of Health and Human Services (HHS); other Federal agencies that, along with HHS, have adopted the Common Rule[1]; State legislatures; health professionals; or others responsible for human subject protections.

This document presents the findings and proposals of a multi-agency Working Group (WG) convened by Office of Science Policy, Office of the Assistant Secretary for Planning and Evaluation to develop a proposed HHS response to the Report. The WG members are listed in Appendix A.

This document has two sections. Part A provides a brief overview of the Report and comments on and responds to some general issues it presents. Part B analyzes and responds to each of NBAC's 21 recommendations.

The WG commends NBAC for its thoughtful and insightful report. The WG agrees that, despite significant improvement in human subject protection during recent decades, difficult issues related to the participation in research of individuals with impaired decisionmaking capacity need further consideration. NBAC has performed a valuable service in bringing attention to these matters.

In developing its recommendations, NBAC systematically addressed the ethical issues raised. It solicited and received a wide range of views from a variety of scientific experts, patient advocates, professional societies, government agencies involved in human subject research, bioethicists, other advisory committees reviewing protections in research on decisional impairment, and many others. NBAC also dedicated a portion of many of its meetings to hearing public testimony. The resulting Report makes a significant contribution to critically important issues in human subject research.

The WG believes, with NBAC, that our goals must be "providing protection for persons with mental disorders while allowing important research to go forward." (Report at 41). This position is in complete harmony with *Mental Health: Report of the Surgeon General,* which emphasizes the "importance of a solid research base for every mental health and mental illness intervention" because "establishing mental health policy on the basis of good intentions alone can make bad situations worse; [whereas] evaluating the practicality and effectiveness of new approaches is efficient and, more critically, is accountable to those for whom an intervention is intended"[2] The WG agrees with many of NBAC's concerns and recommendations and has developed proposals for how HHS might appropriately respond to the Report.

A. GENERAL COMMENTS

NBAC currently is conducting a review of the entire system of human subject protections. The WG recognizes that, upon completing this comprehensive review, NBAC may make additional recommendations affecting human research subjects with impaired decisionmaking capacity. The WG was mindful of that possibility in considering how HHS might address the recommendations contained in the current Report.

Section I addresses a major overall concern regarding NBAC's recommendations - the issue of who should be covered by any additional protections. Section II summarizes NBAC's envisioned regulatory framework and describes the WG's concerns about it and its implications.

I. Scope of Applicability of NBAC's Recommendations

The WG found some ambiguity as to who is to be protected by the Report's 21 recommendations. Certain NBAC recommendations refer to "persons [or subjects] with mental disorders that may affect decisionmaking capacity" (e.g., Recommendations 2 and 20), while others refer to "persons with mental disorders" (e.g., Recommendations 1, 3, and 18). Based upon an analysis of the entire Report, the WG interprets the intended scope of NBAC's recommendations to be "persons with mental disorders that may affect decisionmaking capacity," as listed in the title.

Discussion

The WG agrees with NBAC that research involving persons with mental disorders that may affect decisionmaking capacity merits additional scrutiny and perhaps additional protection. The WG further considered whether Department action should focus just on persons with decisional impairment resulting from a mental disorder or should extend the benefits of additional protections more broadly to all persons with impaired decisionmaking capacity. It concluded that a broader scope is warranted, based on two factors: the need for special protections in a broader population of persons with decisional impairment and the potential for stigmatization (perceived or real) if those special protections are limited to persons with mental disorders that may affect decisionmaking capacity.

a. The scope of the Report's recommendations seem appropriately applicable to all persons with decisional impairment, irrespective of diagnosis.

NBAC focused on persons with mental disorders that may affect decisionmaking capacity[3] "in part because of this population's difficult history of involvement in medical research." (Report at p. ii). Instances of alleged abuse and public and scholarly criticism represented "a critical mass of concern" about the ethics of conducting research, particularly certain drug research, on mental illnesses and about "perceived gaps" in existing procedural protections. (Id. at p. 3). As NBAC noted, the Report continues a history of regulatory recommendations for additional protections in this area.

In the chapter on "Scope,"' the Report states that the definition of mental disorders cannot be precisely pinned down, in part because of rapid changes in the field. The Report lists dementias, delirium, schizophrenia, depression -including bipolar disorder, mental retardation, and substance abuse disorders -as some, but not all, "of the disorders in which decisionmaking capacity may be affected." (Report at p. 7). Nonetheless, other conditions associated with impaired decisionmaking were not included in the scope: "Other potentially vulnerable subjects whose decisionmaking capacity may be compromised by such factors as trauma (e.g., head injury) or physical illness (e.g., cancer or sepsis) will not be considered directly in this report." (Report at p. 2, n.3). However, the Report does not exclude persons with these conditions from the asserted need for additional protections.

The WG agrees with NBAC that current procedures for human subject protection should be improved to adequately protect research participants whose decisionmaking ability is impaired because of a mental disorder. The current HHS and Food and Drug Administration (FDA) regulations rely fundamentally on informed consent and independent review. However, the

protection of informed consent is available only when subjects have the capacity to assess risks and benefits and to choose. Individuals who are decisionally impaired, including some with mental disorders, may not be fully capable of appreciating the range of risks and benefits of a particular protocol. An individual who lacks capacity may only be enrolled in research by a legally authorized representative (LAR); however, if the LAR has a conflict of interest or does not adequately protect the individual's interests or choices regarding research, the individual can do nothing affirmative because of that lack of capacity. Because of the need to rely on surrogate decision-makers and susceptibility to undue influence and coercion, a subject who has impaired decisionmaking capacity' due to a mental condition may not be adequately protected by current informed consent procedures.

However, the Working Group notes that some physical disorders or conditions also may result in impaired capacity to make decisions and therefore to give voluntary informed consent to research. Either mental or physical conditions that impair decisionmaking capacity may make subjects vulnerable to coercion or undue influence and thus in need of protection. As NBAC observed, "many of the issues and concerns raised in this report (and, indeed, many of its recommended protections) could be applied to all persons with questionable or diminished capacity." (Report at p. 5).

b. Limiting the scope of protections may be perceived to be stigmatizing.

Some commentators on the Report believe that focusing on "persons with mental disorders that may affect decisionmaking capacity" improperly stigmatizes a category of persons, most of whom are capable of making their own decisions. Some of the Report's recommendations refer to "persons with mental disorders" without the additional modifier "that may affect decisionmaking capacity" - and this may contribute to the perception of a lack of sensitivity.

Approximately one in five Americans experiences a mental disorder during the course of a year,[4] yet the preponderance are capable of making major life decisions. The WG agrees -- and NBAC's Report takes pains to emphasize -- that a person is not decisionally incapacitated to consent to research merely because that person has a mental disorder or mental illness.[5] However, the Report's focus was not expressly extended beyond persons with mental disorders and that in itself may appear stigmatizing or could lead to inadvertent stigmatization in practice.

c. HHS should treat NBAC's recommendations as potentially applicable to all research subjects whose decisionmaking may be impaired.

NBAC "encourages" use of its Report as "guidance for conducting research on other persons [i.e., in addition to those with mental illness] whose decisionmaking capacity may be impaired." (Report at p. 5). The WG accepts NBAC's suggestion and concludes that the scope of additional protections should encompass all persons with decisional impairment, irrespective of diagnosis.[6] In particular, the WG believes that the Department should extend the safety net of protections to all individuals with a disorder that alters mentation and therefore may adversely affect decisionmaking capacity. However, the WG emphasizes that an individual with a condition that may impair decisionmaking capacity is not necessarily impaired.

In view of the difficulty of determining who is vulnerable as a direct consequence of a condition that impairs decisional capacity, there is no expeditious way to identify, *a priori,* individuals with impaired decisional capacity; yet human subject protections rely primarily on prospective review by investigators and IRBs. Thus, investigators and IRBs should be alerted to those situations that warrant closer scrutiny. To be effective, additional guidance must clearly identify those who are or may be eligible for the additional protection; the IRB should be able to tell when it is reviewing a= protocol

that might encompass that vulnerable population.

Accordingly, 45 CFR §46.401 (a) applies "to all *research involving* children as subjects." Similarly, §46.301 applies "to all biomedical and behavioral *research ... involving* prisoners as subjects." (Emphasis added). In both casts the regulations define who is included in the protected class; although the IRB may need to refer to local law (e.g., the age of majority in the jurisdiction) or ascertain some facts (e.g., whether the proposed subjects are incarcerated) in determining whether the additional protections apply.

NBAC was concerned with a gap in existing regulatory protection for both (1) populations that are vulnerable because of decisional impairment and (2) subjects in certain classes of research that might lead to transient or other decisional impairment. The WG agrees that, in both instances, subjects deserve additional protection. At the same time, the WG recognizes that, in contrast to children and prisoners, it is very difficult to define who is included in the population.

When the concern is with a particular type o f research, the guidance must clearly identify for the IRB what that research is. Given the widespread incidence of mental disorders in the population, many protocols in different fields will -involve subjects with conditions that may affect decisionmaking, even those where the protocol has nothing to do with the study of those conditions and the investigators intend to recruit only adults with decisional capacity. Thus, for example; a protocol studying cholesterol levels or eyewitness testimony -- and including only incidentally a few subjects who experience mild depression or who are recovering alcoholics -- does not necessarily warrant the same degree of scrutiny as would a protocol to study a potential treatment for advanced Alzheimer's disease.[7]

With these factors in mind, the WG concludes that, in assessing NBAC's recommendations, the Department should consider their applicability to research directed toward[8] persons whose mental or physical conditions are associated with decisional impairment. A condition is associated with decisional impairment when there is a reasonable likelihood that (1) the persons sought to be enrolled in the protocol have experienced or may experience decisional impairment as a result of their condition or disorder, or (2) the subjects may become decisionally impaired during the course of the study.

Because some children are also persons whose condition or disorder is associated with decisional impairment, Department action in this area should clearly indicate that it does not supersede the protections of subpart D of 45 CFR Part 46, which regulates research involving children. Further, FDA has a regulation providing an exception to informed consent for subjects in need of emergency medical intervention who cannot give informed consent because of their life-threatening medical condition and do not have an LAR available. See 21 CFR §50.24. HHS announced a comparable waiver of the applicability of the 45 CFR Part 46 requirement for obtaining informed consent for this limited class of research (61 FR 51531, 10/2/96). Thus, any Department action should also clearly indicate that it does not supersede either these protections or the Secretarial waiver.

II. Regulatory Framework Envisioned by NBAC

Many of NBAC's recommendations address the protections contained in existing HHS and FDA regulations. These include recommendations about subject selection, IRB review of research designs, evaluation of risks and benefits, informed consent, increased research and training, and increased support for IRBs. The WG agrees that these are features that may be valuable in protecting subjects whose decisionmaking capacity is impaired. The WG also agrees that increased attention to, and additional guidance in, these areas may be beneficial.

Some of NBAC's recommendations call for HHS and other agencies to require IRBs to implement procedures that are available, but not explicitly required, under current regulations when decisional capacity is an issue. For example, NBAC would encourage, and in some cases require, greater participation on the IRB by individuals familiar with the nature of the disorders and the concerns of the population being studied. Further, for greater than minimal risk research, NBAC recommends that IRBs generally require a formal capacity assessment These are important protections that IRBs already have aiithority to invoke at their discretion, and the WG agrees that IRBs should do so whenever they determine such actions to be necessary and appropriate for the rights and welfare of subjects.

Certain of NBAC's recommendations work in concert to call for a new regulatory framework. This recommended framework would require IRBs to classify all proposed research involving persons with mental disorders that may affect decisionmaking capacity as either (I) minimal risk, (2) greater than minimal risk but offering the prospect of direct medical benefit to subjects, or (3) greater than minimal risk with no prospect of direct medical benefit to the subject. (See Recommendations I0I2). The current regulations do not require a classification of risk.

In accord with the current regulations, the NBAC recommendations would permit any adult who can provide informed consent to choose to participate in IRB-approved research involving any degree of risk. If the person has impaired decisionmaking capacity, the NBAC recommendations would also permit enrollment in the research when the IRB waives the informed consent requirement in accordance with the current regulations. Even without a waiver of informed consent, a person who lacks capacity could be enrolled in minimal risk research (Recommendation 10) by an LAR, provided the LAR meets certain conditions (See Recommendation I4). If the research offers the prospect of "direct medical benefit," then regardless of risk, a person who lacks capacity may still be enrolled in the research by an LAR, subject to the same conditions. (Recommendation 11).

However, if the proposed research does not offer the prospect of direct medical benefit and involves any degree of risk greater than minimal risk, NBAC's envisioned regulatory framework would impose a limit that currently does not exist. (Recommendation 12). The subject could not be enrolled in the research by an LAR, except under one of two circumstances. In addition to IRB approval, either (I) the subject must have executed an advance directive to participate in that type of research, called a "Prospective Authorization" under Recommendation I3 or (2) the research must be reviewed by a "Special Standing Panel" (SSP) convened by the Secretary and that panel must conclude that the protocol "offers the possibility of substantial benefit to the population under study, that its risks to subjects are reasonable in relation to this possible benefit, and that it could not be conducted without the proposed population," and the panel must be "satisfied that all appropriate safeguards are incorporated." (Recommendation 2). If the SSP subsequently were to promulgate guidelines covering certain instances of that type of protocol, then only IRB approval and surrogate consent would be required unless the guidelines require more.

Discussion

a. The envisioned regulatory framework could result in an unnecessarily lengthy review process.

Under NBAC's envisioned regulatory framework, IRBs generally would not be able to approve research without direct medical benefit that poses any risk greater than minimal and involves a person unable to give informed consent, unless that person has executed a Prospective Authorization specifically authorizing this type of research *and* his or her LAR consents. Prospective Authorizations will not provide a significant alternative to SSP review. For some conditions affecting cognition, the individuals do not have, and will probably never have, the decisional

capacity required to execute a Prospective Authorization. Even among those able to execute a Prospective Authorization, very few are likely to do so.

Thus, unless the research offers the prospect of direct medical benefit and regardless of whether it offers the prospect of direct non-medical benefits, the SSP, at least until it has promulgated guidance for IRBs, would be required to review all research involving even a slight increase above minimal risk. Not only physical, but psychological, social, and other non-medical risks must be included in determining the protocol's risk level. Moreover, SSP review would be required for all research supported by HHS where the risk cannot be reduced to minimal risk - i.e., not only for clinical research but also for research in the areas of epidemiology, social and behavioral sciences, program evaluation, health services, and health promotion. This could slow significantly the progress of important research protocols that pose reasonable - albeit greater than minimal - risk.

By contrast, the introduction of an intermediate risk category, as in the HHS children's regulations, Subpart D of 45 CFR 46, along with the ability to consider direct non-medical benefits, would allow IRBs to determine when the risks posed by those protocols are justifiable and what the appropriate' safeguards are, without being required to defer to a national review body. If such an alternative to NBAC's recommendations were adopted, the feasibility of the SSP concept would be materially greater.

b. The envisioned regulatory framework would alter IRB authority in ways that could produce anomalous results.

The Report envisions a framework of protections akin to that of the regulations governing research with children but with some key differences. The following comparison presents two examples.

Section 46.406 of the children's regulations permits the child's parents or guardians to enroll the child in some no-direct-benefit research that "represents a minor increase over minimal risk." For example, if an IRB were to determine that a protocol with no direct benefit posed a minor increase over minimal risk but was "likely to yield generalizable knowledge . . . of vital importance" to understanding or ameliorating autism, a 17-year-old individual with autism could be enrolled with parental consent.

However, the envisioned regulatory framework would not permit even a legally appointed guardian to enroll an adult who lacks decisional capacity in any research with greater than minimal risk and no prospect of direct benefit - unless the potential subject has provided a Prospective Authorization or the research is approved by the standing panel that Recommendation 2 would create (or the IRB is authorized to act in accord with pertinent guidance developed by that panel). Thus, absent the exceptions noted, the same individual at 19 could not be enrolled in that protocol by his or her LAR(s), even by parents who have been formally appointed guardians by the court and would consent; whereas the IRB could approve research that would enrollment that individual at age 17. NBAC's recommendations therefore would limit IRB authority more for the adult than for the child.

A comparison of the safeguards for potentially beneficial research reveals another anomaly. Under §46.405 children may be enrolled in greater than minimal risk research if the research "holds out the prospect of a direct benefit" for the child. By contrast, under NBAC's Recommendation 11, adults who lack decisionmaking capacity may only be enrolled in greater than minimal risk research that "offers the prospect of direct *medical* benefit," which would exclude consideration of other possible benefits to subjects, including psychological, educational or social benefits. (Emphasis added). Thus, the envisioned regulatory framework would narrow the types of benefits that an IRB may consider in determining whether a greater than minimal risk protocol offers a direct benefit.

There are of course important differences between children and adults with impaired decisionmaking capacity. In particular, children are legally presumed to lack decisional capacity, whether or not they do; whereas adults are presumed to possess decisional capacity unless proven otherwise. Also, the individuals who are legally authorized to represent children are more often readily identifiable than those for decisionally impaired adults.

There are also key similarities, e.g., that the degree of actual capacity varies, that State law determines who may represent subjects' interests, and that States may exercise their *parens patriae* power to limit the risk of harm that an LAR may permit. Thus, safeguards for the two groups need not be identical. However, in the opinion of the WG, these factual differences do not justify limiting IRB authority for adults with impaired decisionmaking capacity more than for children in similar situations. The WG is not aware of any evidence that indicates the categories of research risk set up by the children's regulations, which have been in place for 17 years, are unsatisfactory. The WG is also concerned that the existence of two frameworks for approving protocols based on two different sets of risk level may lead to confusion and thus contribute to inadequate compliance by investigators and IRBs.

B. COMMENTS AND PROPOSED ACTIONS ON SPECIFIC RECOMMENDATIONS

This section presents the WG's comments on each of NBAC's 21 recommendations using the order and titles from the Report. Most recommendations are addressed singly, but some are grouped together to facilitate discussion. Each section begins with the text of the recommendation, then presents the WG's analysis, and concludes with the WG's proposed action.

I. Recommendations Regarding Review Bodies

NBAC Recommendation 1: Institutional Review Board (IRB) Membership

All IRBs that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being studied. At least one of these IRB members should be a member of the population being studied, a family member of such a person, or a representative of an advocacy organization for this population. These IRB members should be present and voting when such protocols are discussed. IRBs that only occasionally consider such protocols should involve in their discussion two ad hoc consultants who are familiar with the nature of these disorders and with the concerns of the population being studied; at least one of these consultants should be a member of the population being studied, a family member of such a person, or a representative of an advocacy organization for this population.

Discussion

The WG agrees with the principle, reflected in this NBAC recommendation, that IRB deliberations should include persons who are familiar with conditions that may affect decisionmaking capacity and with the concerns of the population being studied.[9] This principle is particularly important where research involves subjects who may be vulnerable to coercion or undue influence. The presence of these individuals on the IRB, particularly if able to represent the viewpoint and concerns of the population being studied, should contribute significantly to protecting subject rights and welfare.

However, the WG does not endorse the specific recommendation that IRBs be required to include two members (or to engage two consultants) who are knowledgeable about mental disorders and the concerns of the population being studied. Such a specific requirement relative to decisional impairments might set a precedent that would not be practical to implement, especially with respect to other

vulnerable categories of subjects.[10] Rather, the WG considers it preferable that IRBs be afforded the flexibility needed to address the underlying principle of the NBAC recommendation.

The HHS regulations at 45 CFR §46.107(a) and FDA regulations at 21 CFR §56.I07(a) recommend that IRBs that regularly review research involving subjects with mental disabilities include "one or more individuals who are knowledgeable about and experienced in working with these subjects." Nevertheless, the WG shares NBAC's concern that more effective and consistent implementation of this regulation is needed, especially in research involving conditions that may affect decisionmaking capacity.[11]

Proposed Action

The WG proposes that the Office for Human Research Protections (OHRP) - which is the successor to the Office for Protection from Research Risks (OPRR) and is located in the Office of the Secretary, Office of Public Health and Science - working in consultation with FDA, develop and issue interpretive guidance for IRB review of research directed toward persons with mental or physical conditions that are associated with decisional impairment. The WG further recommends that OHRP consider incorporating the following elements in its guidance:

a. That a diagnosis of mental disorder does not necessarily imply decisional impairment relative to research participation; and that certain physical disorders may result in a high likelihood of such impairment.

b. That where an IRB regularly reviews research directed toward persons with conditions that are associated with decisional impairment, the IRB should include members who are familiar with such conditions and with the concerns of the population being studied.

c. That where an IRB only occasionally reviews research directed toward persons with conditions that are associated with decisional impairment, the IRB should involve in its discussion consultants who are familiar with such conditions and with the concerns of the= population being studied.

d. That every effort should be made to include among the IRB members or consultants described in paragraphs 2 and 3 at least one person who has the background, experience, and willingness to serve as an advocate, specifically representing the viewpoint and concerns of the population being studied. Further,

    i That, where appropriate, every effort should be made to engage, as advocates, members of the population being studied. Family members, organization representatives, or others may also serve as advocates where appropriate;

    ii That every effort should be made to ensure that subject advocate IRB members are present when the convened IRB discusses and votes on the proposed research; and

    iii That, where research is eligible for IRB review under expedited procedures, every effort should be made to include appropriate subject advocate IRB members or consultants in the review.

NBAC Recommendation 2: Creation of a Special Standing Panel (SSP)

The Secretary of the Department of Health and Human Services should convene a Special Standing Panel (SSP) on research involving persons with mental disorders that may affect decisionmaking capacity. The panel's tasks should include:

(A) reviewing individual protocols that cannot otherwise be approved under the recommendations described in this report, that have been forwarded by IRBs to the SSP for its consideration. If the SSP finds that a protocol offers the possibility of substantial benefit to the population under study, that its risks to subjects are reasonable in relation to this possible benefit, and that it could not be conducted without the proposed population, then the SSP may approve the protocol if it is satisfied that all appropriate safeguards are incorporated Under no circumstance, however, should the SSP approve a protocol that reasonable, competent persons would decline to enter;

(B) promulgating guidelines that would permit local IRBs to approve protocols that cannot otherwise be approved under the recommendations described in this report. Such guidelines could suggest that a particular class or category of research, using specified research interventions with certain identified populations, could be considered by local IRBs without the need to resort to the SSP for further approval. Under no circumstances, however, should the SSP promulgate guidelines permitting IRBs to approve research that would enroll subjects who lack decisionmaking capacity in protocols that reasonable, competent persons would decline to enter.

The SSP should have members who can represent the diverse interests of potential research subjects, the research community, and the public. The panel's protocol approvals and guidelines should all be published in an appropriate form that ensures reasonable notice to interested members of the public.

Those federal agencies that are signatories of the Common Rule should agree to use the SSP, and the SSP 's effectiveness should be reviewed no later than five years after inception.

Discussion

Under current regulations, IRBs have authority to approve protocols that present greater than minimal risk for decisionally impaired subjects, but promise substantial scientific benefit, *hen the risks are reasonable in relation to the potential benefits. Were IRBs to be stripped of this authority in the case of research that offers no direct medical benefit to subjects, as NBAC recommends (see Recommendation 12), the WG agrees that a mechanism would have to be created to allow acceptable protocols in this category to be conducted. The WG also agrees that guidelines could be valuable to IRBs reviewing protocols that pose moderate risks but require participation by subjects whose decisional capacity maybe impaired, in order for the IRBs to understand, prevent, or alleviate serious problems affecting persons with conditions that may affect decisionmaking capacity.

However, the WG is not persuaded that the SSP is the appropriate mechanism to accomplish either of these functions. As noted in section All above, the WG has serious concerns about the feasibility of the SSP review process in the absence of an intermediate risk category under which IRBs may approve protocols without involvement of a national-level panel.

Even if the envisioned regulatory framework were modified to include an intermediate category of risk, implementation would be inadvisable prior to full consideration of its similarities and differences with respect to the current regulations. For example, whereas the envisioned SSP would have authority to

approve or disapprove protocols, the national-level review panels currently provided for in HHS regulations to oversee certain research involving pregnant women (Subpart B), prisoners (Subpart C), and children (Subpart D)[12] are ad hoc panels that advise the Secretary. Further, preempting the ability of IRBs to approve certain protocols not only would require rulemaking but also would create a precedent that could have an impact well beyond this area.[13] Moreover, since NBAC is currently conducting a comprehensive review of human subject protections, any significant regulatory changes in this areas would be premature until NBAC's further findings and recommendations are available.

NBAC intended the SSP "to provide some genuine flexibility to respond to new knowledge and to create greater uniformity of understanding" in an area of disagreement about how to achieve the proper balance between advancing knowledge and protecting vulnerable subjects. (Report at p. 55). The WG agrees that both of these goals are important but notes that two IRBs reviewing similar . protocols may appropriately come to different conclusions because of local differences - as where one IRB is considering more restrictive State laws or is more confident about the investigator's sensitivity to decisional impairment issues. Whether establishing a national panel with approval authority is the proper way to balance concerns about uniformity and flexibility in this area requires a more thorough public discussion.

Proposed Action

As outlined in the discussion following Recommendations 10-12, the WG proposes that the Department solicit additional public input on whether, and how, a national-level panel should be implemented to protect the rights and welfare of human research subjects whose conditions are associated with decisional impairment.

II. Recommendations Regarding Research Design

NBAC Recommendation 3: Appropriate Subject Selection

An IRB should not approve research protocols targeting persons with mental disorders as subjects when such research can be done with other subjects.

Discussion

The WG agrees with NBAC's intent; this recommendation is consistent with the "basic ethical principles" of respect for persons, beneficence and justice -- as identified in the Belmont Report by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In particular, the recommendation applies the justice principle to subject selection. These principles are currently embodied in the HHS regulations in §46.111 (a)(3) and the FDA regulations in §56.111(a)(3): "Selection of subjects is equitable:... the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."

The WG shares NBAC's view that it is inappropriate to engage in research persons who are decisionally impaired simply because, for example, their condition provides investigators easier access to subjects who are unlikely to object. Due consideration must be given to the appropriateness and scientific value of conducting the proposed research with subjects who can provide informed consent. However, this recommendation should not be interpreted to preclude

specific categories of research with persons who are decisionally impaired even when that research is possible with those who can consent but is likely not to be scientifically practical or sufficient. Some research that literally "can be done with other subjects" and sometimes should be done first with other subjects, cannot be conducted equally well with subjects who can provide informed consent in those instances where crucial information cannot be obtained without the participation of the same types of subjects who are ultimately going to receive the intervention or otherwise benefit from the research. Investigators and IRBs must carefully weigh the appropriateness of recruiting persons with decisional impairment in studies in terms of both the scientific question and subject concerns.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, develop and issue interpretive guidance clarifying how these concerns should be addressed within the existing regulations.

NBAC Recommendation 4: Justifying Research Design and Minimizing Risks

Investigators should provide IRBs with a thorough justification of the research design they will use, including a description of procedures designed to minimize risks to subjects. In studies that are designed to provoke symptoms, to withdraw subjects rapidly from therapies, to use placebo controls, or otherwise to expose subjects to risks that may be inappropriate, IRBs should exercise heightened scrutiny.

Discussion

The WG agrees that "investigators should provide IRBs with a thorough justification of the research design they will use, including a description of procedures designed to minimize risks to subjects." NBAC has rightly called attention to the importance of considering research design. Although current regulations do not explicitly require investigators to justify their research designs, the information is necessary for IRBs to make the determinations required under §46.111(a)(1)-(2) of the HHS regulations and 21 CFR §56.111(a)(1)-(2) of the FDA regulations. The IRB must ensure that risks to subjects "are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk" and "are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result." Since the investigator is in the best position to provide justification for the research design, the regulation implicitly requires the investigator to provide this information.

The WG is concerned, however, that some may mistakenly read the last sentence of Recommendation 4 together with some of the accompanying text as implying that protocols designed to provoke symptoms, to withdraw subjects from therapies, or to use placebo controls are inherently unethical. These designs may sometimes expose subjects to heightened risk and, therefore, warrant greater scrutiny by IRBs, rigorous justification by investigators, and particularly close attention to the subjects in the study. However, they are not inherently unethical; and the WG does not agree with the possible implications stemming from the use of the word "otherwise" in the second sentence. It should also be appreciated that study designs that are inadequate to provide useful information are unethical.[14]

The WG also agrees that IRBs should ensure that all research designs are justified by a positive risk-benefit analysis and that subjects will be fully informed of the risks involved, including those stemming from assignment to a placebo group in clinical research. "An analysis of each case depends on the validity of standard treatment, on the seriousness of the disease, the burden of the intervention, and some

fundamental value questions about whether the risks are worth the possible benefits."[15] As NBAC points out, it may be worthwhile to remind IRBs that they are required to make these determinations and to minimize risks as fully as possible for all research covered by the HHS and FDA regulations, especially research involving vulnerable populations.

Proposed Action

The WG proposes that OHRP, working closely with FDA on matters of study design, issue such additional interpretive guidance as it considers necessary to implement this Recommendation in accordance with the foregoing discussion.

NBAC Recommendation 5: Evaluating Risks and Benefits

Investigators should provide IRBs with a thorough evaluation of the risks and potential benefits to the human subjects involved in the proposed protocol. The evaluation of risks includes the nature, probability, and magnitude of any harms or discomforts to the subjects. The evaluation of benefits should distinguish possible direct medical benefits to the subject from other types of benefits.

Discussion

The WG strongly supports this recommendation. Although current regulations do not explicitly require investigators to provide this information, the information is necessary for IRBs to carry out their obligations under §46.111 of the HHS regulations and §56.111 of the FDA regulations - i.e., that risks to subjects (1) be minimized and (2) be reasonable in relation to (a) the anticipated benefits, if any, and (b) the importance of the knowledge that may reasonably be expected to result. In the text following the recommendation, NBAC recognizes that the requirements are implicit in the regulations: "This recommendation reaffirms what is already in the federal regulations....": (Report at p. 56).[16] IRBs typically request this information. Thus, the recommendation seems to promote the efficient operation of IRBs. As the text following the recommendation emphasizes, "The assessment should include consideration of the particular procedures proposed and their relationship to the specific conditions of the individuals who may be involved as study subjects." (Report at p. 56).

Although the investigator is required to provide risk assessment information, the recommendation does not excuse the IRB from making its own independent assessment and evaluation as to whether the protocol should be approved under the Department's regulations and guidelines. As NBAC notes, "IRBs should be alert to the possibility that researchers and subjects may not evaluate the risks and benefits of a particular study in the same way." (Report at p. 56). Participation of "individuals who are knowledgeable about and experienced in working with these subjects," in accordance with §46.107(a) of the HHS regulations and §56.107(a) of the FDA regulations, may assist the IRB in making its independent assessment. See above regarding Recommendation 1.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, issue such additional interpretive guidance as it considers necessary to implement this Recommendation.

III. Recommendations Regarding Informed Consent and Capacity

NBAC Recommendation 6: Informed Consent

No person who has the capacity for consent may be enrolled in a study without his or her informed consent. When potential subjects are capable of making informed decisions about participation, they may accept or decline participation without involvement of any third parties.

Discussion

The WG fully supports this recommendation. Informed consent is the bedrock principle that makes the enterprise of human research permissible. Soliciting informed consent respects the research subject's autonomy. It also enables the subject to make an informed choice about the risks and benefits of research. Informed consent is a cornerstone of the HHS and FDA regulations.- This recommendation is consistent with those regulations. See 45 CFR § 46.111(a)(4) and § 46.116 (except where the IRB may waive consent, "no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative") and 2I CFR §56.111 (a)(4) and §50.20, respectively. To be legally effective, consent by the subject requires that the subject have the capacity to consent; conversely, decisionmaking by the subject's surrogate is effective only when the surrogate is legally authorized to provide consent under State law and the subject lacks capacity to consent.

NBAC noted and the WG agrees that, where the existing regulations permit waiver of informed consent, this recommendation does not negate that waiver.

Proposed Action

No action is needed.

NBAC Recommendation 7: Objection to Participation in Research

Any potential or actual subject's objection to enrollment or to continued participation in a research protocol must be heeded in all circumstances. An investigator, acting with a level of care and sensitivity that will avoid the possibility or the appearance of coercion, may approach people who previously objected to ascertain whether they have changed their minds.

Discussion

The WG agrees with this recommendation. Under the HHS and FDA regulations, participation by subjects is voluntary, and subjects may discontinue participation at any time. 45 CFR §46.116(a)(8) and 21 CFR §50.25(a)(8). Thus, investigators must heed a subject's objection to participation that is articulated in any manner. Similarly, investigators must heed a subject's objection to any intervention or procedure in the protocol. It is important to determine carefully whether the subject is objecting to a particular procedure in a study or to participation altogether. If the former, it may be possible to continue the study without the particular procedure, or if not, to re-approach the subject with care, as NBAC suggested. Investigators and IRBs must minimize the risk of coercion or undue influence before and throughout the trial, particularly in approaching vulnerable subjects, who previously objected, to ascertain whether they have changed their minds. 45 CFR §46.111(b) and 21 CFR §56.111(b). Guidance clarifying the right of individuals with decisional impairment to object to participation may be helpful to investigators and IRBs.

Further, the WG emphasizes that investigators must take care to minimize risks to any subject who is withdrawing from the study. Moreover, if at any time there is ambiguity regarding the subject's

willingness to participate, investigators must err on the side of subject safety and autonomy.

Proposed Action

The W G proposes that OHRP, working in consultation with FDA, issue such additional interpretive guidance as it considers necessary to implement this recommendation.

NBAC Recommendation 8: Assessing Potential Subjects' Capacity to Decide about Participating in a Research Protocol

For research protocols that present greater than minimal risk an IRB should require that -an independent, qualified professional assess the potential subject's capacity to consent. The protocol should describe who will conduct the assessment and the nature of the assessment. An IRB should permit investigators to use less formal procedures to assess potential subjects' capacity if there are good reasons for doing so.

Discussion

The WG recognizes that accuracy about the subject's capacity to provide informed consent is a prerequisite to respect for persons and to compliance with the HHS and FDA regulations.[17] Adopting this recommendation would create a strong presumption that IRBs should require formal capacity assessment for all greater than minimal risk research in this area, although NBAC notes that IRBs may forego requiring a capacity assessment "if there are good reasons for doing so." However, a requirement, even a presumption, that capacity must be assessed is problematic.

Under the regulations, obtaining valid informed consent from a subject necessarily requires that the subject have capacity under both the law of the jurisdiction and the regulations. See 45 CFR §46.116(a) and 21 CFR §50.20 ("no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject"). Determining that the subject has capacity and can give legally effective consent is primarily the responsibility of the investigator, who must also apply the local standard to avoid liability exposure for treatment without informed consent. Under the current regulations, the IRB is also responsible; for it must determine that the investigator's protocol satisfies State and Federal informed consent requirements. See 45 CFR §46.11I (a)(4) & (b) and 21 CFR §50.I11 (a)(4) & (b).

NBAC recommends that a formal capacity assessment be required in almost all cases, rather than at the IRB's discretion. Although the WG recognizes the importance of accurate capacity assessment, requiring a formal assessment would be problematic and premature for a number of reasons. As NBAC recognizes, most persons with mental disorders that may affect decisional capacity in fact have decisional capacity. The same is true of other conditions associated with decisional impairment. Thus, a requirement, even a presumption, that capacity be formally assessed would often be unnecessary, and the WG is concerned it could contribute to the lingering stigmatization of persons with mental disorders.[18] Moreover, the need to ensure that the subject has capacity to consent is not unique to this area and thus will have wider implications.[19]

Requiring a formal capacity assessment is also problematic and premature because there are no known, accurate, and validated capacity assessment instruments for clinical care, let alone research participation. There is also no consensus regarding the professional qualifications necessary to perform capacity assessments. Determining whether the person performing the assessment can be "independent" is also problematic if he or she is paid by the researcher or is otherwise affiliated with the

institution; IRBs would need to have a clearer definition before this requirement could be implemented. Moreover, the standard for legal capacity to consent must be determined under local laws, which are not uniform. When crucial issues are unresolved -- such as who should perform the assessment, what is the proper assessment instrument, and according to what standard for capacity, it would be inappropriate for the Department to require formal capacity assessments.

Under the current regulations, IRBs remain responsible for determining that every protocol satisfies State and Federal informed consent requirements and are given the authority to impose any additional safeguards they deem necessary, including a formal capacity assessment.[20] In selecting the appropriate safeguards, the IRB may consider the potential subjects' condition, the degree of impairment, the complexity of the protocol, the degree of risk involved, the research design, the phase(s) of the research when capacity is most at issue, and the IRB's assessment of the investigator's ability to provide accurate and ethical capacity assessment. Especially given the many unsettled factors in current capacity assessment practices, the WG concludes that IRBs should continue to have discretion to determine in each case whether capacity assessments or other safeguards are warranted.

However, the WG recognizes that there is substantial room for improvement in the way that IRBs handle the informed consent process. Working with subjects whose decisionmaking capacity may be impaired is an additional complication to adequately addressing informed consent. Thus, ensuring the adequacy of informed consent in general is crucial to protecting vulnerable subjects.

The WG agrees with NBAC's recommendation that NIH support research to expand knowledge about the most appropriate methodologies for assessing decisionmaking capacity so they may become available to researchers. NIH has already taken several steps to increase research and prioritize studies focused on human subject issues. See Appendix B.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, issue such additional interpretive guidance as it considers necessary to enhance the way in which investigators and IRBs address the informed consent process, in general, as well as when decisional impairment is an issue.

NBAC Recommendation 9: Notifying Subjects of Incapacity Determinations and Research Enrollment

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her LAR to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. Should the person object to participating, this objection should be heeded.

Discussion

The WG agrees with the principles embodied in this recommendation but would emphasize them differently. Respect for persons includes a potential subject's right to object to a determination that he or she lacks capacity, to object to the proposed involvement of third parties, and to object to any participation in research.[21] Belmont Report at § C.1. Whether or not the person has the capacity to give informed consent, he or she is entitled to object, without the involvement of third parties, to participation or continuation in research. This right to object is implemented in current regulations, 21 CFR 50.25(a)(8).[22]

Providing a potential subject with notice and opportunity to object to a determination that may lead to unwanted involvement by others or enrollment in research by another is a necessary prerequisite to showing respect for persons and therefore crucial to these rights.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, issue such additional interpretive guidance as it considers necessary to implement this recommendation.

IV. Recommendations Regarding Categories of Research

Recommendations 10-12 are discussed together.

NBAC Recommendation 10: Research Protocols Involving Minimal Risk

An IRB may approve a protocol that presents only minimal risk, provided that:

(A) consent has been waived by an IRA pursuant to federal regulations; or

(B) the potential subject gives informed consent; or

(C) the potential subject has given Prospective Authorization, consistent with Recommendation 13, and the potential subject's LAR gives permission, consistent with Recommendation 14; or

(D) the potential subject's LAR gives permission, consistent with Recommendation 14.

NBAC Recommendation 11: Research Protocols Involving Greater than Minimal Risk that Offer the Prospect of Direct Medical Benefit to Subjects

An IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefit to the subject, provided that:

(A) the potential subject gives informed consent; or

(B) the potential subject has given Prospective Authorization, consistent with Recommendation 13, and the potential subject's LAR gives permission, consistent with Recommendation 14; or

(C) the potential subject's LAR gives permission, consistent with Recommendation 14. The research must also comply with Recommendations 7, 8, and 9.

NBAC Recommendation 12: Research Protocols Involving Greater than Minimal Risk Research that Do Not Offer the Prospect of Direct Medical Benefit to Subjects

An IRB may approve a protocol that presents greater than minimal risk but does not offer the prospect of direct medical benefit to the subject, provided that:

(A) the potential subject gives informed consent; or

(B) the potential subject has given Prospective Authorization, consistent with Recommendation 13, and the potential subject's LAR gives permission, consistent with Recommendation 14; or

(C) the protocol is approved by the panel described in Recommendation 1, or falls within the guidelines developed by the panel, and the potential subject's LAR gives permission, consistent with Recommendation 14.

The research must also comply with Recommendations 7, 8, and 9.

Discussion

The WG agrees with the principle, reflected in NBAC's Recommendations 10, 11, and 12, that additional safeguards are warranted when research is directed toward subjects with mental or physical conditions that are associated with decisional impairment. This principle is consistent with current requirements of the HHS regulations at 45 CFR §46.111(b) and the FDA regulations at 21 CFR §56.111(b).

However, as detailed in the next section on Recommendation 13, the WG believes that widespread execution of Prospective Authorizations for research is unlikely. Moreover, the large number of proposed protocols that Recommendation 12 would require to be reviewed by the SSP could make this recommendation impractical to implement. (See analysis in section A.II.a above).

The WG senses substantial polarity of opinion within the research and ethics communities regarding the involvement of subjects with decisional impairment in greater than minimal risk research that presents no prospect of direct benefit to the individual subject. Some have asserted that such research cannot be justified under any circumstances. Some have argued that certain important, greater than minimal risk research may be justifiable only in terms of "future benefits to others who have or will develop the condition or disorder" under study, or that prohibiting such research "would contribute to needless suffering." (See, e.g., NIH, *Interim - Research Involving Individuals with Questionable Capacity to Consent: Points to Consider,* Appendix C). Others have asserted that certain non-treatment research (e.g., laboratory studies involving lumbar punctures or CT scans with contrast; population-based epidemiology studies), while presenting somewhat more than minimal physical, psychological, or social risk to subjects, may be justified if appropriate protections are provided to safeguard subjects' rights and welfare. Still others question why NBAC limited its consideration to the prospect of direct *medical* benefit to subjects, especially with regard to nonmedical research, without considering possible psychological or social benefits.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, solicit additional public comment regarding appropriate approval standards as a function of differing levels of risk in research directed toward subjects with mental or physical conditions that are associated with decisional impairment. The WG proposes in particular that a formal Federal Register solicitation request comment on appropriate mechanisms for ensuring needed protections; appropriate regulatory frameworks for characterizing informed consent and IRB approval requirements as a function of differing levels of risk; and acceptability of certain overarching principles.

a. With respect to mechanisms, the solicitation could invite comment on at least three alternatives:

   i. best practice consensus building

ii. OHRP/FDA guidance; and iii rulemaking;

b. With respect to the regulatory frameworks for review of research protocols that would involve decisionally impaired subjects but offer no prospect of direct benefit to them, the solicitation could invite comment on at least three alternative approaches:

i. leaving discretion with the cognizant IRB - in accord with current regulations and guidance such as the NIH "Points to Consider" (Appendix C);

ii. establishing a regulatory structure similar to that used in the children's regulations, 45 CFR 46.406 - i.e., introducing a concept such as "minor increment above minimal risk"; authorizing IRBs, with appropriate guidance, to approve research protocols in this risk category as well as the "minimal risk" category, but requiring that IRBs defer to a national-level panel regarding research protocols that present "more than a minor increment above minimal risk"; and

iii. establishing the regulatory structure recommended by NBAC in the Report.

c. With respect to overarching principles, the solicitation could invite comment on at least the following candidates:

i. Additional safeguards are needed for all HHS-conducted, HHS-supported, or HHS-regulated research that is directed toward subjects with mental or physical conditions that are associated with decisional impairment.

ii. Additional safeguards that should be considered include: the use of independent consent monitors, independent assessment of the subject's capacity to consent, advance research directives or prospective research authorizations, waiting periods, and special communication techniques. In general, safeguards should be commensurate with the degree of risk, the nature of the risk, the complexity of the research, and the degree of the subjects' impairment.

iii. For all research involving subjects with mental or physical conditions that are associated with decisional impairment, any subject's objection to any research procedure or intervention or to participation in research should be honored.

iv. Minimal risk research should be permitted if (a) the legally effective informed consent of the subject or the subject's LAR is obtained, or (b) informed consent requirements may be waived in accordance with Subpart A of 45 CFR Part 46.

v. Greater than minimal risk research that presents the prospect of direct benefit to the individual subject should be permitted if (a) the relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternative approaches; and (b) the legally effective informed consent of the subject or the subject's LAR is obtained. In determining whether a protocol presents a prospect of direct benefit to the subject, the IRB may consider medical, psychological, social, or other benefits that it deems relevant and meaningful.

vi. Greater than minimal risk research that presents no prospect of direct benefit to the individual subject should be permitted if (a) the legally effective informed consent of the subject or the subject's LAR is obtained; (b) the research only presents experiences that are (i) likely to be identical to, or reasonably equivalent to, experiences inherent in the target

population's actual medical, dental, psychological, social, or educational situation; and (ii) consistent with accepted professional standards relative to the target population; (c) appropriate additional safeguards are included to protect the rights and welfare of the subjects; and (d) the research is likely to yield important generalizable knowledge about the subject's disorder or condition.

vii. Other research or classes of research presenting greater than minimal risk without- - prospect of direct benefit to the individual subject should be permitted if the Secretary, after consultation with a panel of experts, determines that (a) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of persons with mental or physical conditions that arc -associated with decisional impairment; (b) the research will be conducted in accordance with sound ethical principles; and (c) the legally effective informed consent of the subject or the subject's LAR will be obtained.

V. Recommendations Regarding Surrogate Decisionmaking

NBAC Recommendation 13: Prospective Authorization

A person who has the capacity to make decisions about participation in research may give Prospective Authorization to a particular class of research if its risks, potential direct and indirect benefits, and other pertinent conditions have been explained. Based on the Prospective Authorization, an LAR may enroll the subject after the subject has lost the capacity to make decisions, provided the LAR is available to monitor the subject's recruitment, participation, and withdrawal. The greater the risks posed by the research protocol under consideration, the more specific the subject's Prospective Authorization should be to entitle the LAR to permit enrollment.

Discussion

The WG agrees that an advance directive for research, such as NBAC's "Prospective Authorization," where permitted by State or other applicable law, can be extremely useful in some circumstances. For example, a valid Prospective Authorization may be useful and feasible if executed prior to enrollment in a protocol during which decisionmaking capacity may become impaired or by a person who has been diagnosed with a degenerative disorder, such as Alzheimer's disease.

However, the recommendation will not prove useful to most subjects whose conditions are associated with decisional impairment. First, individuals who have never had capacity will be unable to execute a Prospective Authorization.

Second, it is unlikely that Prospective Authorizations will be executed by a significant number of individuals. Most States authorize advance directives for end-of-life medical care (such as a living will or a durable power of attorney), yet few individuals use them, even though most patients are informed of this option and provided with forms by their health care facilities. Since individuals would be more motivated to indicate preferences regarding end-of-life care than to indicate preferences regarding involvement in research without direct benefit, Prospective Authorizations will seldom play a role in this area of research.

Finally, because of the degree of specificity suggested in the recommendation's explanatory text, it is extremely unlikely that a validly executed Prospective Authorization will be effective, except for those executed immediately before the subject's enrollment in a protocol. Due to scientific progress, research

designs and interventions are constantly evolving; consequently, the ability to predict the attendant risks and benefits will diminish over time.

The WG agrees with NBAC that autonomous choices, made while capable, to cover future periods of mental impairment or incapacity should be respected. When a loss of decisional capacity is foreseeable, investigators should encourage subjects to consider how their wishes regarding research may be carried out; and IRBs should consider the necessity of this safeguard. Any advance directive rejecting a research intervention must be heeded. With regard to advance directives to participate in research, investigators must observe local laws regarding their validity and effect.[23]

All or nearly all the States recognize the right of individuals with capacity to have their wishes regarding health care carried out after a loss of capacity, particularly where the wishes are formalized in an advance directive. However, the WG is not aware of any State that has recognized the validity of an advance directive for research. It would be helpful to IRBs, investigators and subjects if the States addressed the issue of advance directives for research. Until then, Federal action regarding such a Prospective Authorization would not be productive; although, as addressed below in connection with Recommendation 17, ascertaining the wishes of subjects for whom impairment of capacity is foreseeable may be beneficial.

Proposed Action

The WG proposes that the Secretary make the States aware of NBAC's Recommendations and our proposed actions and encourage the States to consider them, by sending copies of NBAC's Report and this Analysis to the States' Attorneys General.

Recommendations 14-16 are discussed together.

NBAC Recommendation 14: Legally Authorized Representatives

An LAR may give permission (within the limits set by the other recommendations) to enroll in a research protocol a person who lacks the capacity to decide whether to participate, provided that:

(A) the LAR bases decisions about participation upon a best estimation of what the subject would have chosen if capable of making a decision; and

(B) the LAR is available to monitor the subject's recruitment, participation, and withdrawal from the study; and

(C) the LAR is a person chosen by the subject, or is a relative or friend of the subject.

NBAC Recommendation 15: Expansion of the Category of Legally Authorized Representatives and of the Powers Granted under Statutes for Durable Powers of Attorney (DPA) for Health Care

In order to expand the category of LARs:

(A) an investigator should accept as an LAR, subject to the requirements in recommendation 14, a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place.

(B) states should confirm, by statute or court decision, that:

(1) an LAR for purposes of clinical decision making may serve as an LAR for research; and

(2) friends as well as relatives may serve as both clinical and research LARs if they are actively involved in the care of a person who lacks decisionmaking capacity.

NBAC Recommendation 16: State Legislation Regarding Advanced Directives for Research

States should enact legislation, if necessary, to ensure that persons who choose to plan for future research participation are entitled to choose their LAR.

Discussion

The WG agrees with NBAC that determining who may serve as an LAR and how the LAR should make decisions is important to research involving persons whose conditions are associated with decisional impairment. The current regulations recognize and implement the principle that State law controls on the issue of who may provide consent for a decisionally-impaired individual to participate in research.[24] The NBAC recommendations also appear to recognize this principle, but it is not clear that NBAC accounted for all the potential conflicts between State law and Federal requirements or for the State-Federal coordination problems inherent in its recommendations.

Recommendation 14 suggests an amendment to the regulations that would define "Legally Authorized Representative" to include "a person chosen by the subject, or [who) is a relative or friend of the subject," and those who may serve as surrogate decision-makers for health care. In the absence of a valid and effective Prospective Authorization, NBAC's framework would extend the authority of LARs to enroll subjects only to minimal risk research or to research where there is a prospect of direct benefit, unless the protocol has been approved by the SSP of Recommendation 2. Otherwise, where research involves greater than minimal risk and does not hold out the prospect of. direct benefit, the authority of the LAR would apparently extend only to permitting continued enrollment or withdrawing the subject. It is not clear how these recommendations would relate to State laws, which may be more or less restrictive.

Because issues surrounding the authority of a surrogate to act on behalf of another are the province of State law, investigators must comply with both local law and the Federal regulations.[25] There are no potential conflicts or coordination problems so long as Federal requirements are in addition to State law requirements, or vice versa. However, if the State and Federal requirements are discordant, researchers would face the dilemma of jeopardizing their Federal funding or subjecting themselves to potential liability under State law. Recommendation 14(B), referring to the LAR's availability to monitor the subject's participation in the research, could be implemented in addition to State law requirements. However, 14(A) and (C) propose Federal requirements that may be contrary to State law. 'This is apparently recognized in Recommendation 15(B), in which NBAC recommends that State law be amended to be consistent with Recommendations 14(C) and 15(A). Except for Recommendation 14(B), implementing NBAC's recommendations as Federal requirements for LARs would be dependent upon action by the States.

Recommendations 15 and 16 are not directed to the Department. However, as NBAC recognized, State laws would have to change in order for the other recommendations regarding LARs to be operational. Not all States have addressed the issue of who may act as an LAR in the absence of an advance directive. Those that have addressed the issue have only identified LARs for making health care treatment decisions.

However, the WG notes that one State that has tried to address research involving persons with decisional impairment, including LAR issues, has now abandoned that effort. Maryland's Assistant Attorney General recently wrote a letter stating that the "effort at finding common ground must be reckoned a failure." "With some opponents damning the bill as unacceptably onerous and others as unacceptably weak, committee, approval would have been most unlikely. Therefore, our effort to pursue this legislation has ended. The legal status quo, unsatisfactory as it is will remain."[26]

Despite such potential difficulties, it would be helpful to IRBs, investigators and subjects if the States addressed the issue of research LARs both under, and in the absence of, advance directives.

Proposed Action

The WG proposes that the Secretary make the States aware of NBAC's recommendations and our proposed actions and encourage the States to consider them, by sending copies of NBAC's Report and this Analysis to the States' Attorneys General.

NBAC Recommendation 17: Involving Subjects' Family and Friends

For research protocols involving subjects who have fluctuating or limited decisionmaking capacity or prospective incapacity, IRBs should ensure that investigators establish and maintain ongoing communication with involved caregivers, consistent with the subjects' autonomy and with medical confidentiality.

Discussion

The WG agrees that - when a research protocol involves a subject with fluctuating decisionmaking capacity, limited decisionmaking capacity, or prospective decisionmaking incapacity - anticipatory discussions among the subject, the investigator(s), caregiver(s), and/or other concerned parties could contribute materially to the subject's safety and welfare during the course of the research. The WG agrees further that, when fostering such discussions, investigators and IRBs are obliged to be mindful of the subject's autonomy, the confidentiality of information, and the requirements of applicable statutes.[27]

The WG does not endorse the specific recommendation that IRBs be *required* to "*ensure* that investigators *establish and maintain* ongoing communication with involved caregivers."[28] (Emphasis added). In view of the inherent difficulty of achieving a consensus on the definition of such core concepts as "involved caregiver" and "consistent with the subject's autonomy and medical confidentiality," development of an effective regulatory requirement seems likely to involve a challenging and possibly protracted rulemaking process. Moreover, implementation of requisite procedures to ensure that appropriate communication is established and maintained would impose new burdens of effort, time, and costs upon IRBs at a time when many of them frequently are hard-pressed to discharge their current functions.

The WG believes that, where the subject might be expected to lose decisionmaking capacity during the research, temporarily or permanently, investigators should solicit the subject's preferences regarding communications with, and involvement of, caregivers or other concerned parties prior to commencement of the study. Under 45 CFR §46.111(b) and 21 CFR § 56.111(b) an IRB may so require, if it determines that safeguard is warranted for a particular protocol.

Proposed Action

The WG proposes that OHRP, working in consultation with FDA, issue such additional interpretive guidance as it considers necessary to implement this recommendation in accordance with the foregoing discussion.

VI. Recommendations Regarding Education. Research, and Support

NBAC Recommendation 18: Reviewing and Developing Educational Materials Regarding Research

Professional associations and organizations should develop (or review their existing) educational materials pertaining to research involving persons with mental disorders to ensure that they are adequate to inform the health care community and the public of ethical issues related to the involvement of such persons as research subjects, and to convey the importance of measures to ensure that their rights and we fare are adequately protected

Discussion

This recommendation is not directed at the Department. However, the WG endorses this recommendation for all conditions that may cause decisional impairment and commends it to these associations and organizations for consideration.

Proposed Action

No Departmental action is needed.

NBAC Recommendation 19: Expanding Knowledge about Capacity Assessment and Informed Consent

The National Institutes of Health (NIH) should sponsor research to expand understanding about decisionmaking capacity, the best means for assessing decisionmaking capacity, techniques for enhancing the process of informed consent, and the possible roles of surrogate decision makers in research. It should sponsor research to evaluate the risks of various research interventions, and the attitudes of potential subjects toward the prospect of participating in research. Particular attention should be paid to attitudes toward participating in research of greater than minimal risk that does not offer the prospect of direct medical benefit to subjects. These data may be of particular value to the panel described in Recommendation 2.

The NH should ensure that proposals for training grants and center grants include appropriate provisions for training and technical assistance in the issues discussed in this report. Where appropriate, NIH and OPRR should consider using consensus development conferences or workshops to advance discussion of these issues.

Discussion

The WG agrees with NBAC on the need for research and training in the area of human subject protections in general and the area of protecting vulnerable subjects in particular. The NIH appreciates NBAC's acknowledgment of its support for research and training in informed consent, research ethics, and issues associated with decisional impairment. HHS is currently conducting many activities that address the concerns outlined in this recommendation.

One of the most important of the activities in this area is the **NIH Program Announcement on Research on Ethical Issues in Human Studies,** which was released March 31, 1999 (PA NUMBER: PA-99-079) and is ongoing. This PA is designed to encourage empirical studies that are expected to fill many gaps in our knowledge and understanding of the complex ethical issues that arise when involving human participants in research. Some possible research topics include:

> Evaluate the cognitive ability required to comprehend, appreciate, and reason in order to consent to specific experimental procedures and risks; to differentiate between research and standard treatment; and to distinguish between discretionary and obligatory activities (e.g., quid pro quo add-on studies or wraparound studies).
>
> Develop and test new means of sustaining autonomy to be used in situations of declining or loss of capacity, means can include current yet untested advance directives for research and consent programs for organ donation (e.g., durable power of attorney, proxy, legally authorized representative).
>
> Investigate how potential participants weigh risks and benefits, e.g., what factors would lead individuals to participate in studies that present significant risk with little or no prospect of direct benefit.
>
> Apply existing knowledge from cognitive, behavioral, social, and educational fields to develop practical, reliable, valid, and efficient methods and instruments for assessing capacity to comprehend, appreciate and/or reason in a research setting, especially when individuals with cognitive, psychiatric, and developmental disorders are involved; the focus should be on functional abilities rather than on clinical diagnosis.

Some additional NIH research and training activities are highlighted below. Details on these and other NIH and CDC activities can be found in appendix B.

Research Activities

> NIH/DOE/VA Request for Applications on Informed Consent to identify and validate methods for improving the informed consent process in scientific research..
>
> The National Institute on Deafness and Other Communication Disorders Working Groups on (1) Considerations for Developing and Implementing Genetic Diagnostic Tests for Hereditary Hearing Impairment and Other Communication Disorders (December 1998) and (2) Communicating Informed Consent to Individuals- Who Are Deaf or Hard-of Hearing (May 1999).
>
> Clinical Center Department of Clinical Bioethics.
>
> ORWH/NCI/NAPBC/PRIM&R/ARENA Meeting, "Informed Consent and IRB Review: A Model for Review and Discussion."

Training Activities

> NIH/CDC/HRSA/AHCPR/SAMHSA Mentored Scientist Development Award in Research Ethics-Program Announcement

National Institute of Mental Health "Investigators Guide." Informed Consent

Working Group [1997-99].

NIMH "Participants Guide to Clinical Mental Illness Research."

Office of Intramural Research/NIH Committee on Scientific Conduct and Ethics.

In addition, the WG is aware that the OHRP is initiating an aggressive effort to educate research investigators, IRB members, and relevant staff. OHRP will work closely with HHS agencies to ensure that all personnel involved in the conduct or administration of research receive appropriate training related to human subject protection and informed consent, including issues related to capacity assessment.

Proposed Action

The WG proposes that the Secretary charge the Director of NIH to determine and take whatever additional action is needed in this area.

NBAC Recommendation 20: Institute of Medicine Review of Research Studies

The Department of Health and Human Services should contract with the Institute of Medicine (IOM) to conduct a comprehensive review and evaluation of the nature and extent of challenge, washout, and placebo controlled studies with subjects with mental disorders that may affect decision making.

Discussion

The WG agrees with NBAC that these study designs may expose subjects to additional risk and therefore warrant heightened scrutiny. Data, guidelines and other resources may be helpful to investigators, IRBs, and others reviewing research supported by the Department, who must determine when these study designs are justifiable. The WG notes that the National Institute of Mental Health (NIMH) has already taken substantial steps regarding these concerns. In December 1998, NIMH sponsored a workshop on "Medication Discontinuation and Symptom Challenge Designs," bringing together scientists, bioethicists, consumers, family advocates, HHS regulatory staff, and Congressional staff Based on this, the National Advisory Mental Health Council created a special Council Workgroup on Human Subject Research to consider "fundable" grant applications involving potentially problematic human protection issues. This group, acting since July 1999 via the Council, has had a substantial effect on assuring that risk/benefit evaluations, informed consent, and clinical safeguards are properly considered. The NIMH is also involved in discussions regarding the appropriate use of placebo controls, access by research participants to useful clinical information after a clinical trial, and other key issues.

The NIMH will continue to take steps to better safeguard human research volunteers upon whom clinical research depends - both to monitor studies and to anticipate emerging issues in research involving potentially vulnerable populations. In addition, OHRP will work with all components of the Department to enhance protections for human subjects.

Proposed Action

The WG proposes that the-Secretary charge the Director of NIH, in consultation with the OHRP Director and the FDA Commissioner, to determine and take whatever additional action is needed in this area.

NBAC Recommendation 21: Increased Funding to Support Necessary Protections of Human Subjects

Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (government, private sector enterprises, and academic institutions) should work together to make these resources available.

Discussion

The WG recognizes that IRB burdens continue to expand and agrees that IRBs need additional resources to support them in protecting human subjects. This recommendation has been made by the Office of the Inspector General (OIG),[29] others, and now NBAC. The OIG concluded that "[a]s they have for about 25 years, IRBs continue to provide vital protections for human subjects,"[30] but found them to be vulnerable for a number of reasons, particularly the dramatic increase in IRB workloads,[31] while "staffing levels and budgets have remained the same at many IRBs." In addition, "[m]anaged care cost pressures have constrained the time that IRB members have to devote to reviewing protocols.... With limited personnel and few resources, IRBs are hard pressed to give each review sufficient attention."[32] Thus, the OIG recommended that IRBs be provided with sufficient resources to be able to effectively carry out their function."[33]

The WG agrees with NBAC's recommendation. Some institutions have increased support for IRBs, but "[m]any IRBs are not sufficiently supported by their institutions."[34] Not all institutions may have the ability to increase funding to IRBs without causing detrimental effects elsewhere within the institution.

IRBs reviewing protocols from commercial sponsors are free to request full reimbursement of the costs of IRB review, although this opportunity appears to be underutilized. Institutions conducting Federally-sponsored research are able to seek reimbursement for IRB expenditures through indirect cost payments that are a regular part of research awards.

Proposed Action

The WG proposes that the Department continue to work with awardee institutions to increase the financial support available to IRBs.

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[1] Most federal agencies that conduct or support research involving human subjects have adopted regulations based on the language set forth in Subpart A of 45 CFR 46. This set of common regulations is referred to as the Federal Policy (Common Rule) for the Protection of Human Subjects. The FDA regulations at 21 CFR Parts 50 & 56 are FDA's equivalent to the Common Rule.

[2] Mental Health Report, Executive Summary p. viii.

[3] "[T]he primary concern of this report is with the potential effect of neurologic or psychiatric conditions on the decisional capacity of potential research subjects." Report at p. 20. "The specific concern of this report, however, is with persons whose decisional impairments may be related to the presence of what we currently understand to be a mental disorder." *Id.* Part of NBAC's limiting its focus in this way may result from its conclusion that additional steps needed to be taken to "both enhance existing protections *and facilitate broad public support for continued research on mental disorders."* Harold T. Shapiro, Letter transmitting the Report (January 8, 1999) (emphasis added).

[4] Mental Health Report, Executive Summary, p. xii.

[5] For example, at pages 5-6, the Report states:

> NBAC was mindful of the concerns that could arise from a focus on individuals who are members of a group (i.e., persons with certain mental disorders) rather than on persons who share a common functional characteristic (i.e., questionable decisionmaking capacity). This focus could raise the specter of equating mental disorders with incapacity and thus potentially stigmatize these individuals. NBAC shares this concern and recognizes that not all persons with mental disorders have impaired decisionmaking capacity.
>
> To assume that a diagnosis of a mental disorder implies that a person is incapable of deciding whether to participate in a research protocol is prejudicial and incorrect.... Although persons with mental disorders are not necessarily decisionally impaired, much less decisionally incapable, any evidence that places a person's decisionmaking ability into question should trigger a clinical assessment Any disorder that alters mentation may adversely affect decisionmaking ability ....

[6] Concerns have been raised about the need for input from communities that would be affected most by the expansion of the recommendations 'scope. No particular action is needed to, address those since *any* proposed Departmental action should provide ample opportunity for comment by the public.

[7] Although "NB AC principally focused its attention on those who may be primarily considered for research protocols because it is their particular mental disorder that is being studied" (Report at p. 5), NBAC's recommendations encompass more than such protocols. Even within the field of mental disorders, NBAC's scope would include protocols about a condition that may cause impairment, even if it is improbable that the subjects will be decisionally impaired (because, for example, their condition is only mild, or at an early stage).

[8] See, e.g., Subpart B of the Regulations, which appears to be concerned with both research involving pregnant women as subjects and research "activities directed toward pregnant women." § 46.201 (a)(2) and the heading of § 46.207.

[9] The Emergency Research Regulations provide precedent for the mode of consultation envisioned by NBAC; see 21 CFR §50.24(a)(7): "consultation ... with representatives of the communities in which the clinical investigation will be conducted and from which subjects will be drawn."

[10] See endnote 19 re: subpart B proposal.

[11] If the IRB determines that including such individuals is necessary to protect the subjects, then HHS and FDA regulations (45 CFR §46.111(b) or 21 CFR §56.111(b)) seemingly require their inclusion.

[12] Under 45 CFR §46.407, parents or guardians are permitted to enroll a child in research that presents more than a minor increase over minimal risk, provided that, after the Secretary consults a panel of experts and allows for public review and comment, the Secretary finds that "the research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children" and that "the research will be conducted in accordance with sound ethical principles."

[13] Moreover, public discussion is also warranted by existing disagreements on whether persons with decisional impairment may be involved under any circumstances in *any* research having greater than minimal risk and no prospect of direct benefit - even with review by a national panel.

[14] Report at p. 9 ("respectful treatment begins with soundness in research design, which is the *sine qua non* for ethical research involving human subjects"). Also see Office for Protection from Research Risks (OPRR) - IRB Guidebook, Ch. IV - Considerations of Research Design, Part A: "Me value of research depends upon the integrity of study results .... [I]f a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study."

[15] See, e.g., testimony/statement of Dr. Norman Fost before the Pediatric Advisory Subcommittee, a Subcommittee of the FDA Anti-infective Drugs Advisory Committee, Ethical Issues Day I, November 15, 1999.

[16] NBAC also intends the recommendation to facilitate the IRB's determination of risk levels.

[17] At least one State appeals court has suggested that the same constitutional requirements that must be observed before the involuntary administration of anti-psychotic drugs also apply to enrolling children, or adults who lack capacity, in greater than minimal risk research without benefit to the *subject. T.D. v. N. Y. Office of Mental Health*, 650 N.Y.S.2d 173 (N.Y. Appellate Division 1996). Those requirements include notice to the subject, or a surrogate, and the opportunity to object at a judicial or an administrative hearing to both the capacity determination and the intervention. On appeal, New York's highest court disapproved of the appeal court's foray into constitutional analysis after it had already determined that the regulations were invalid on the narrower legal grounds that the promulgating body had no authority to issue those *regulations. T.D. v. N. Y. Office of Mental Health*, 91 N.Y.2d 860, 690 N.E.2d 1259 (1997). As a result, the intermediate court's constitutional analysis carries no legal weight; the higher court did not weigh in on the substance of the constitutional analysis.

[18] For example, the self-esteem of subjects who become aware that their capacity is being questioned may suffer. Even if the assessment is handled in a confidential and sensitive manner, the fact that the subject's capacity has been assessed may have implications outside the research protocol; for example, the subject may be asked on a job or security application if his or her capacity has ever been tested or questioned.

[19] As an example see, in response to comments received on the proposed changes to Part B, HHS noted the following:

> The Department notes that *ensuring that information is understood and checks for understanding tailored to particular situations are not precluded by the regulations, nor are they unique to research with pregnant women.* Subpart A affords IRBs the opportunity and the authority to ensure the adequacy of informed consent and protections by imposing additional requirements or monitoring the research or consent process.

[20] The HHS regulations at 45 CFR §46.111(b) and FDA regulations at 21 CFR § 56.111(b) already require that research involving subjects with mental disabilities include additional safeguards to protect the rights and welfare of those subjects. Some other safeguards available to IRBs include: requiring modification of the informed consent process so as to empower the subject to decide whether to enter or continue in a research study, requiring that LARs be educated about the research in order to better perform their duties, and monitoring of the consent process or the research. Another issue not settled by NBAC's recommendation is *when* capacity assessments most be performed, particularly when capacity is expected to fluctuate over time. The IRB may determine that an ongoing safeguard such as monitoring would be more effective than discrete capacity assessments.

[21] See also endnote. 17.

[22] In fact, the FDA further recognized the importance of this right in the emergency research regulations. "If a legally authorized representative or family member [of a subject who lacked capacity at the time of the emergency] is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible." 21 CFR §50.24(b).

[23] Some states may permit LAR's, even in the absence of a Prospective Authorization, to enroll subjects in certain types of research based on substituted judgment.

[24] The regulations define the term "legally authorized representative" to mean "an individual or judicial or other 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 CFR § 46.102(c) and 21 CFR §50.3(1).

[25] Sections 46.116 and 50.20 provide that, except as otherwise provided in 45 CFR Part 46 or 21 CFR Part 50, respectively, no investigator may involve a human being as a subject in research covered by the regulation, "Unless the investigator has obtained the *legally effective* informed consent of the subject or the subject's *legally authorized* representative." (Emphasis added).

Guidance on consent by a legally authorized representative is provided in "Interim-Research Involving Individuals with Questionable Capacity to Consent: Points to Consider" (http://grants.nih.gov/grants/policy/questionablecapacity.htm) under the heading "Use of a Surrogate." This statement was developed to assist IRBs and clinical investigators in protecting research participants who are, may be, or may become decisionally impaired by NIH in consultation with a broad array of experts on, and participants in, clinical research, bioethics, mental health, substance abuse, and age-related conditions, as well as agencies and groups concerned about clinical research and human subject protections. According to the statement, "where permitted by law, individuals with impaired capacity may have a family member or other legally authorized representative serve as a surrogate for research decisions, with this role documented during the consent process." The surrogate should make research decisions based on substituted judgment whenever possible. Otherwise, best interest standards are to be used if the values of the individual are not known or cannot be given legal effect. The statement also emphasizes the importance of surrogates receiving some education about their own role and the cognitive and health status of the research participant, as well as about the study in which the participant may be involved.

[26] Letter of Maryland Assistant Attorney General Jack Schwartz to Gary Ellis (February 7, 2000).

[27] A number of findings of the Surgeon General's Mental Health Report, are particularly relevant:

> State and Federal laws protect the confidentiality of health care information but are often incomplete because of numerous exceptions which often vary from state to state. Several states have implemented or proposed models for protecting privacy that may serve as a guide to others.
>
> States, consumers, and family advocates take differing positions on disclosure of mental health information without consent to family caregivers. In states that allow such disclosure, information provided is usually limited to diagnosis, prognosis, and information regarding treatment, specifically medication.
>
> When conducting mental health research, it is in the interest of both the researcher and the individual participant to address informed consent and to obtain certificates of confidentiality before proceeding. Federal regulations require informed consent for research being conducted with Federal funds.
>
> ****
>
> Until the stigma associated with mental illnesses is addressed, confidentiality of mental health information will continue to be a critical point of concern for payers, providers, and consumers.

Executive Summary, page xviii.

[28] An issue of some controversy in mental health is whether families should be provided information regarding their adult child in certain circumstances....

> Family advocates often take the position that a family in a caregiving role should have access to some types of information whether or not the individual specifically has consented to the disclosure, because it is necessary to play a caregiving role (Lefly, 2000). Advocates for

> consumer-recipients often argue that consent should be required, because the right to confidentiality belongs to the recipient of services, and because there may be intrafamily conflicts that could be exacerbated by the release of information to family members.

Surgeon General's Mental Health Report Chapter 7 at ___.

[29] OIG, ***Institutional*** *Review Boards: A Time for Reform* (OEI-01-97-00193) June 1998, at p. 4.

[30] *Id*

[31] The IRBs studied "reported average increases of 42 percent in initial reviews during the past 5 years, with the result that some of them are reviewing more than 2,000 protocols. At the same time, these IRBs are being deluged with adverse event reports from the multi-center trials they oversee." *Id* at p.5.

[32] *Id* at 6. "The resources we refer to are, above all, the human resources represented by staff and board members, but also space, computers, and other elements essential to an efficient and effective IRS." *Id*. at p. 19.

[33] *Id.* at p. 19.

[34] OIG, ***Institutional*** *Review Boards:* Promising *Approaches* (OEI-01-97-00191) June 1998, at p. 1.

APPENDIX A

WORKING GROUP ON THE NBAC REPORT: *RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY*

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The Working Group thanks Dr. Charles McCarthy, former Director of the Office for Protection from Research Risks, and Dr. David Shore, National Institute of Mental Health, for providing important background information regarding regulatory considerations and decisionmaking capacity assessment, respectively.

APPENDIX B

DHHS Research and Training Activities Addressing Protections of Human Subjects

A. NIH Research Activities

1. **NM Program Announcement on Research on Ethical Issues in Human Studies, (highlighted in response to #19) which was released March 11, 1"9 (PA NUMBER: PA-99-079).** This PA is designed to encourage empirical studies that are expected to fill many gaps in our knowledge and understanding of the complex ethical issues that arise' when involving human participants in research. Some possible research topics include:

   - Evaluate the cognitive ability required to comprehend, appreciate, and reason in order to consent to specific experimental procedures and risks; to differentiate between research and standard treatment (e.g., therapeutic misconception); and to distinguish between discretionary and obligatory activities (e.g., quid pro quo add-on studies or wrap-around studies).

   - Develop and test new means of sustaining autonomy to be used in situations of declining or loss of capacity; means can include current yet untested advance directives for research, and consent programs for organ donation (e.g., durable power of attorney, proxy, legally authorized representative) and especially novel and innovative approaches.

   - Investigate how potential participants weigh risks and benefits e.g., what factors would lead individuals to participate in studies that present significant-risk with little or no prospect of direct benefit.

   - Apply existing knowledge from cognitive, behavioral, social, and educational fields to develop practical, reliable, valid, and efficient methods and instruments for assessing capacity to comprehend, appreciate and/or reason in a research setting, especially when individuals with cognitive, psychiatric, and developmental disorders are involved; the focus should be on functional abilities rather than on clinical diagnosis.

2. **The National Institute on Deafness and Other Communication Disorders Working Groups.** One December 8, 1998, the Working Group on Considerations for Developing and Implementing Genetic Diagnostic Tests for Hereditary Hearing Impairment and Other Communication Disorders considered the role of genetic testing as it pertains to the research community engaged in the study of the genetics of hearing. Issues needing attention by these communities before such testing should be considered include informed consent. On May 25, 109, the National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH), convened a day-long working group on "Communicating Informed Consent to Individuals Who Are Deaf or Hard-of-Hearing," in Bethesda, Maryland. The purposes of the meeting were: (1) to clarify issues of informed consent; (2) to develop guidelines for use by scientists who are recruiting deaf or hard of hearing individuals to participate in clinical research; (3) to highlight materials for the scientific community to use in facilitating clear communication between deaf or hard-of-hearing research volunteers and scientific investigators in clinical research; and, to propose new, needed materials for improving communication about informed consent.

3. **NIH/DOE/VA RFA on Informed Consent.** On September 27, 1996, NIH, DOE, and DVA issued a jointly sponsored Request for Applications (RFA) entitled, "Informed Consent in Research Involving Human Participants." Sponsored Institutes were NCI, NHGRI, NIA, NIAAA, NIAID, NICHD, NIDA, NIMH, and NINR The goal of the RFA is to identify and validate methods for improving the informed consent process in scientific research. Eleven grants were funded. This RFA followed a July 1995 **NIMH Program Announcement (PA) on Informed Consent,** entitled, "Informed Consent in Clinical Mental Health Research," to encourage research in this area

4. **Clinical Center Department of Clinical Bioethics.** The Department serves several functions, including conducting research on clinical and research related bioethics issues. The Department is currently conducting research on reasons for participation in clinical trials. A survey study is being developed on motivation for

subject participation in clinical research. The study will begin with CC research participants and expect to be expanded to multiple centers. Plans are also being made to conduct further research on informed consent.

5. **ORWH/NCI/NAPBC/PRIM&R/ARENA Meeting, "Informed Consent and IRB Review: A Model for Review and Discussion."** On June 2, 1997, the National Action Plan on Breast Cancer, Public Responsibility in Medicine and Research, the Applied Research Ethics National Association, the National Cancer Institute and the NIH Office of Research on Women's Health cosponsored a meeting titled "Informed Consent and IRB Review: A Model for Review and Discussion." The National Action Plan on Breast Cancer presented a model for obtaining specimens for research, as well as principles to be used by IRBs in reviewing protocols that propose to use human tissues, and a model consent form for obtaining human tissues from routine surgical procedures. The meeting participants discussed and commented upon the model and principles, and made suggestions for the practical application of this model.

B. NM Training Activities

1. **NIH/CDC/HRSA/AHCPR/SAMHSA Mentored Scientist Development Award in Research Ethics-Program Announcement** Released on January 22, 1999 and sponsored jointly with CDC, HRSA, AHCPR and SAMHSA, this award will support training in research ethics for health professionals working at academic and other health-related institutions in biomedical, behavioral, or public health research, particularly research involving human participants. This initiative follows a directive from the Secretary of Health and Human Services in response to President Clinton's apology to the survivors and relatives of the men who participated in the Tuskegee Syphilis Study. The directive requires DHHS agencies to offer training - with special outreach to minority scientists for post-graduate training in research ethics and for the development of short courses in research ethics.

2. **National Institute of Mental Health *Investigators Guide.*** Through a contract with the American Psychiatric Association (APA), NIMH developed an investigators' resource manual that addresses a wide range of ethical issues in clinical research. The manual is envisioned as a "working tool" for clinical investigators. The manual explores the pros and cons of various approaches to responding to the concerns of all parties in the research process. It was published by APA in 1999. *Ethical Issues in Psychiatric Research: A Resource Manual on Human Subjects Research.* edited by Pincus, Lieberman, and Ferris.

3. **Informed Consent Working Group.** During the period of 1997-99, the NCI, together with OPRR and FDA, sponsored an Informed Consent Working Group that developed recommendations and a template for writing informed consent documents that are simpler and easier to understand. The recommendations and template are being used by investigators nationally and have been distributed to all IRBs with multiple project assurances. Workshops have been held with investigators at national meetings and with IRB members at PRIM&R.

4. **National Institute of Mental Health *Participants Guide to Clinical Mental Illness Research.*** The guide is for participants in clinical mental research and their families. The guide includes an overview of the clinical research process, a discussion of ethical and legal issues in research, questions patients should ask and consider before participating as a research subject, and information about obtaining results of studies in which individuals have participated. An ad hoc group of advocacy organizations were brought together to discuss the contents of the Guide. The Guide can be found at the URL: http://www.nimh.nih.gov/studies/clinres.htm

5. **Office of Intramural Research/NIH Committee on Scientific Conduct and Ethics.** The Committee on Scientific Conduct and Ethics is composed of a broad spectrum of members from the Institutes and Centers. The committee was established in September 1995 and its charge includes: developing and/or refining the existing Guidelines for the Conduct of Research; developing Guidelines for Training and Mentoring; developing effective mechanisms for ethics training for the NIH scientific community, including the ethics column in the NIH Catalyst. The third edition of the Guideline for the Conduct of Research (http://www.nih.gov/news/irnews/guidelines.htm) was published in 1997. The Guidelines for Training and

Mentoring are being developed now. Training of facilitators to lead ethics case discussions, developed by NHGRI (http://www.nhgri.nih.gov/about_nhgri/dir/ethics/message.html) are underway.

6. **Trans-NIH - Training in the Responsible Conduct of Research.** Every predoctoral and postdoctoral National Research Service Award (NRSA) trainee supported by an institutional training grant must receive training in the responsible conduct of research. Grant applications must include a description of a program to provide formal or informal instruction in scientific integrity on the responsible conduct of research. Programs are encouraged to include topics such as: conflict of interest, responsible authorship, policies for handling misconduct, policies regarding the use of human and animal subjects, and data management. More details are provided in the *NIH Guide for Grants and Contracts,* Volume 21, Number 43, November 27, 1992.

7. **NIH/CDC/HRSA/AHCPR Program Announcement on Short-Term Courses in Research Ethics.** Bioethics Training Initiative. The National Institutes of Health (NIH), Centers for Disease Control (CDC), Health Resources and Services Administration (HRSA), Substance Abuse and Mental Health Services Administration, and the Agency for Health Care Policy and Research (AHCPR) invite applications for grants to develop, conduct, and evaluate short-term courses on ethical issues in research, particularly those involving human participants. Courses should improve the skills of biomedical, behavioral, social science, and public health researchers in identifying and addressing *the* ethical, legal, and social implications of their research, especially when human participants are involved. Courses developed include Ethics Course on ScientistParticipant Partnerships, Ethical Issues in International Research, and Ethics of Research Participation in Vulnerable and Special Populations.

8. **Office of Intramural Research/NIH Computer-Based Training for NIH Researchers.** Protecting Human Subjects in the NIH Intramural Research Program. This computer-based training module was developed to orient NIH research staff to the special requirements associated with research involving human subjects. Completion of this training is required by NIH staff who contemplate involvement with this type of research. The training is also available for download and use by staff in other organizations beyond the NIH. The training can be found at: http://helix.nih.gov:8001/ohsr/newcbt/

9. **NIH Bioethics Interest Group Website.** Interest group includes participants from the intramural and extramural communities at NIH. Topics addressed have included: research with the decisionally impaired, bioethics training, and end-of-life issues. Website contains resources on bioethics issues for easy access by NIH staff: http://www.nih.gov/sigs/bioethics/index.html

10. **National Institutes of Environmental Health Sciences Research Ethics Program.** The Office of the Scientific Director supports several programs designed to promote responsible conduct in research. Located within the Division of Intramural Research at the National Institute of Environmental Health Sciences (NIEHS), the Office coordinates educational activities, training workshops, and conferences on ethical issues in environmental health research. The Office of the Scientific Director works closely with the NIEHS Institutional Review Board, the Office of Clinical Research, the Office of the Director, and the NIEHS Division of Extramural Research to develop institutional policies that promote research integrity. The Office also conducts interdisciplinary research on ethical, legal, and social issues in environmental health research, spanning such fields as environmental toxicology, cancer research, and environmental genomics.

11. **National Institutes of Health (NIH) And The Food and Drug Administration (FDA) National Human Subject Protections Education Workshop Program.** The NIH and the FDA are continuing to sponsor a series of workshop on responsibilities of researchers, Institutional Review Boards (IRBs), and institutional officials for the protection of human subjects in research. The workshops are open to everyone with an interest in research involving human subjects. The meetings should be of special interest to those persons currently serving or about to begin serving as ‘a member of an IRB. Issues discussed at these workshops are relevant to all other Public Health Service agencies. Upcoming workshops include: “Human Subjects Research & IRBs Under Fire” “Cultural Diversity in Clinical Research” “Ethical Research in the New Millennium: What the Belmont Report Didn’t Anticipate” and “Protection of Human Subjects: Involving Special Populations.”

C. CDC Training Activities

1. **Office of the Director/CDC Computer-Based Training for CDC Researchers.** *Scientific Ethics* training for CDC researchers involved in intra- and extramural research. *Scientific Ethics* was launched on February 17, 1999. This computer-based training program, designed in five discrete modules, was developed to familiarize CDC scientists and other public health professionals with basic ethical principles, policies, and procedures for the responsible conduct of science. All scientific staff and managers are required to complete the training within six months of its introduction to their respective Centers/lnstitute/Offices (CIO). New staff members will be required to complete the training before they conduct research at CDC or ATSDR. The program is a self-directed learning opportunity that allows users to exit and re-enter at will, choose areas of greatest personal interest, and select levels of complexity through optional exercises. The five modules: CDCs Mission in Science, Protection of Human Subjects, Scientific Integrity, Science-related Responsibilities, and Case Studies, can be studied in any order. *Scientific Ethics* may be accessed via the CDC Intranet. A CD-ROM disk is available for staff in remote locations. A passing score on the certifying exam included in *Scientific Ethics* will trigger the program to print a personalized certificate to which a unique identifier will be assigned. This identifier will also be required on requests for Institutional Review Board-approval of research involving human participants.

2. **CDC Corporate University Science Survival Skills Course.** A 40 hour introductory course for CDC scientists engaged in research has been developed by the Office of the Associate Director and the Epidemiology Program Office to enhance scientists' knowledge of the CDC policies and procedures involved in the conduct of science. Sessions on scientific integrity, misconduct, human subjects research, authorship and manuscript clearances policies and procedures are included. In addition, a mock Institutional Review Board (IRB) meeting is conducted with the students serving as IRB members. CME, CNE, and CEU credits are offered upon successful completion of the course.

3. Scientific **Ethics Seminar Series.** During 2000 and 2001, the Office of the Associate Director for Science will host a seminar series designed to stimulate thought on ethical issues CDC researchers encounter while conducting both domestic and international public health research. The goals of the series are to introduce ethical topics of broad concern within CDC, provide updated information on new ethical issues, and to facilitate a networking opportunity for CDC researchers to later share, debate and discuss related experiences. Each seminar will be two hours long, have a public health theme, and be conducted by an experienced researcher, philosopher, ethicist or a combination of these individuals. The format for each seminar will vary, some will involve panel discussions with panelists taking opposing views. All will provide time to question and interact with the speaker/panelists.

4. **"Brown Bag" Seminars on Human Subjects Research.** The Office of the Associate Director for Science sponsors a series of "brown bag" seminars throughout the year which are designed to educate CDC scientists on human subjects issues. CDC's Human Subjects Public Health Educator and CDC's Human Subjects Manager regularly team up to present various human subjects-related topics at branch and division meetings.

5. **International Ethics Working Group.** The Office of the Associate Director for Science and the Office of Global Health have formed a working group of CDC researchers interested in the area of ethical issues related to CDC's international health activities. The purpose of the working group is to discuss CDC responsibilities and needs in the area of international ethics in relation to its mission and to identify activities that can help CDC effectively accomplish this mission.

6. **International Human Subjects Research Web Page.** This page (http://www.cdc.gov/od/ads/ihsr/index.htm) was designed to keep CDC investigators involved in international researcher involving human subjects and collaborators abreast of international ethical codes and guidance documents; organizations involved in international human subjects research; articles of interest in international ethics; and meetings, conferences and training opportunities. In addition to English, many documents may be found in Spanish, French and Russian.

7. **Joint CDC/University International Bioethics Fellowship Program.** Discussions are underway with a

local university to co-sponsor an international bioethics fellowship program. Such a program could provide an opportunity for CDC collaborators in developing countries to develop leadership skills in bioethics, and for CDC and its partner to facilitate critical dialogue on the topic.

8. **Annual IRB Training.** Each January CDC conducts an all-day training session primarily for new IRB members; however, all IRB members are encouraged to attend. In addition, CDC has invited IRB members from Morehouse School of Medicine and Life University to participate. Topics include the Federal regulations for protecting human subjects (45CFR46) and assurances of compliance with 45CFR46. During the afternoon, a mock IRB meeting is held. About two months later, a make-up training day is held for IRB members unable to attend the January session. Interested investigators are invited to attend the make-up session.

   CDC's IRB chairs also have instituted a mentoring program where seasoned IRB members mentor new IRB members. Further, seasoned lRB members are also available to sit with investigators to provide one-on-one training in developing protocols that involve human subjects.

9. **IRB Training for Community Partners.** CDC has been invited by a number of state health departments to provide IRB training.

10. **Human Subjects Web Page.** The Associate Director for Science hosts a Human Subjects home page (http://www.cdc.gov/od/ads/hsr2.htm) Highlights include:
    - **a.** ***Guidelines for Developing a Consent Document.*** Developed by a former CDC IRB Chair, this guide helps the investigator write consent documents at the 8th grade reading level. The guide is also useful to find standard wording for various parts of a consent document.
    - **b.** ***Protocol Development Checklist.*** The checklist helps guide the investigator to think about what should go into a research protocol. It is used to prompt the investigator to include all items that may apply to the proposed research. Not all items may apply, however. In addition, *a* ***Human Subjects Supplement*** to the checklist is included as the Protocol Development Checklist does not include items that pertain to research involving human participants. The ***Human Subjects Supplement*** checklist helps the investigator think about what should go into the human subjects part of a research protocol, when applicable.
    - **c.** ***Informed Consent/Assent Checklist*** This checklist helps guide the IRB and investigator when developing ALL research protocols involving human participants. A separate column is for use when developing assent forms.
    - **d.** ***Vulnerable Populations Checklists.*** Three separate checklists help guide the IRB and investigator in addressing issues of added safeguards for research targeting pregnant women, fetuses, and in vitro fertilization or involving prisoners or. children.

D. CDC Reports on Human Subject Participation in Research

1. **Participation of Women, Minorities and Children in CDC-Conducted Research**. A report entitled **An *Evaluation of the Participation of Women, Minorities and Children in CDC-Conducted Research*** *was* recently completed and distributed to all CDC CIOs. The report discusses the status of CDC's inclusion of women, minorities and children in research in light of federal policies adopted in the 1990s to ensure that under represented populations are included in federally supported research. The CDC report was undertaken to (1) determine how well CDC is implementing its policy to include women and minorities in research and (2) determine whether a need exists to develop a formal policy to include children in research. The report is available on the Internet at http://www.cdc.gov/od/ads/hsr2.htm.

2. **State Statutes Addressing the Inclusion of Children in Research.** The Office of the Associate Director for Science and the Office of General Counsel are nearing completion on a comprehensive report all U.S. State statutes on the involvement of children in research. In addition, the report will define the age of majority for each state and provide a point-of-contact. Once complete, the report will be available on the Internet at http://www.cdc.gov/od/ads/hsr2.htm.

APPENDIX C

Interim - Research Involving Individuals with Questionable Capacity to Consent: Points to Consider

Importance of Research Involving Individuals with Impaired Decisionmaking Capacity.

Research is essential to improve our understanding of and ability to treat human diseases and disorders that place great burdens on individuals and their families. The quest for new knowledge, however, should never take precedence over the welfare of the research participant. Research may at times involve individuals with limited decisionmaking capacity. The NIH is committed to helping researchers and Institutional Review Boards (IRBs) carry out this research in an ethical manner, protecting the rights and welfare of research participants while advancing treatment opportunities and vital knowledge. Critical to this research process are appropriate safeguards that ensure legally effective[1] informed consent and protect the confidentiality and dignity of the individuals participating in research.

Individuals in a wide variety of situations may have impaired decisionmaking capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally impaired. Some research questions may only be answered by research that involves persons with impaired decisionmakng capacity; precluding this research would contribute to needless suffering. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. While this area is controversial, limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual participant but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non-therapeutic approaches may benefit subsequent generations.

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired. While limited decisionmaking capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny by IRBs and researchers is warranted for research involving this population.

In developing this statement, members of several NIH Institutes consulted a broad array of experts on clinical research, bioethics, mental health, substance abuse, and age-related conditions. The Office for Protection from Research Risks and representatives from professional and lay advocacy communities, former research participants and IRB members, and others concerned about clinical research and human subject protections also provided valuable perspectives. Together, we have carefully considered clinical research situations in which the additional safeguards described in the DHHS regulations for the protection of participants in research[2] might be used by IRBs and by clinical investigators to protect potentially vulnerable individuals.

The NIH offers the following Points to Consider to assist IRBs and clinical investigators in their effort to protect participants in research who are, or may be, or may become decisionally impaired:

Conflicting Roles and Potential Conflicts of Interest Potential and actual research participants, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic, and possibly creating confusion among participants and their families.

It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical investigator.

IRB Membership. IRBs that regularly review research involving vulnerable subjects (such as the decisionally impaired) are required by DHHS and FDA regulations to consider including one or more individuals who are knowledgeable about and experienced in working with these subjects (45 CFR 46.107; 21 CFR 56.107). When

reviewing research involving individuals with questionable capacity to consent, additional options in the makeup of the IRB should be considered:

- Include at least one voting member, independent of the research and investigators, with appropriate professional background, knowledge and experience in working with individuals with questionable capacity;

- Include additional voting members from the community; these members may include representatives of patient advocacy groups and others not affiliated with the research institution.

Assessing Capacity to Consent. Individual's capacities, impairments, and needs must be taken into account, in order to develop practical and ethical approaches to enable them to participate in research. Since well-validated and practical methods to assess capacity to consent are clearly needed, the NIH is supporting and will continue to support research addressing these issues. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research *methodology,* is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in participants' decisionmaking is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

- Limited decision making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent

- Both IRBs and clinical investigators must keep in mind that decisionmaking capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing.

Responsibilities of Investigators and IRBs:

Not all research projects proposing to involve decisionally impaired persons should be approved by IRBs, and indeed, not all such persons should be enabled to participate in research studies.

- Principal investigators and members of the research team bear primary responsibility for protecting research participants. Responsibilities of IRBs also are significant, including the review of the informed consent forms and processes and research design as presented in the research proposal. They should exercise heightened vigilance in the review of protocols involving individuals with questionable capacity in accordance with 45 CFR 46.111(b).[3]

- As impairment increases, along with risks and discomforts, safeguards should increase according to a sliding scale, i.e., protections should be proportional to the severity of capacity impairment, or to the magnitude of experimental risk, or both. Provisions for additional safeguards should be in place prior to involving individuals with questionable decisionmaking capacity in research that poses greater than minimal risk.

- Educational efforts should be ongoing to enhance research participants' understanding and appreciation of their role in the research.

Options for Additional Safeguards. A sliding scale involving assessment of risks, benefits, and capacity to consent should guide the IRB's decisions regarding additional safeguards. Many strategies are available as options for investigators as they develop their research protocols and for IRB members as they evaluate them. In considering increasing levels of risk and/or impairment, investigators should be creative in choosing appropriate protections, seeking strategies used successfully in other situations.

- **Use of an Independent Monitor.** When reviewing greater than minimal risk research involving

individuals with questionable capacity to consent, IRBs should discuss and document the potential value of an independent monitor. A monitor can be appointed to be present when investigators invite individuals with impaired decisionmaking capacity to participate in a research study. The consent process should be visible throughout, and IRBs have a right to observe recruitment, assessment, the informed consent process, and debriefing of research participants (and/or their family/surrogates).

- **Use of a Surrogate.** Where permitted by law, individuals with impaired capacity may have a family member or other legally authorized representative serve as a surrogate for research decisions, with this role documented during the consent process. Surrogates should be informed of the risks, benefits, and alternatives to the research when they are providing permission for an individual to participate. Whenever possible, surrogates should make research decisions based on substituted judgment, reflecting the views of the individual expressed while decisionally capable. Best interest standards should be used if the values of the individual are not known. It is important that surrogates receive some education about their own role, the cognitive and health status of the research participant, as well as about the study in which the participant may be involved.

- **Use of Assent in Addition to Surrogate Permission.** The autonomy of individuals with impaired decisionmaking capacity should be respected. Their assent to participation in research should be obtained whenever possible and their decision to withdraw from a study at any time should be honored.

- **Use of an Advance Directive.** Where State or other applicable law permits, use of an advance directive for research may be considered.

- **Use of Informational/Educational Techniques.** Because informed consent is an ongoing process throughout the course of the protocol, assessing and enhancing comprehension at each stage is essential. Single sheet summaries of important information about key elements of a study may be useful when provided on a regular basis. Questions from potential participants and family members should be encouraged, and handouts of frequently asked questions and answers regarding specific human subject protections can be prepared. Model consent forms and procedures can be developed. Communication between members of the research team and participants and their families is key to successful research participation.

- **Use of Waiting Periods.** Individuals who are decisionally impaired may need more time to consider the information they are given about a research protocol. Information should be provided incrementally to facilitate understanding_ planning built-in waiting periods within the consent process also may be useful to allow potential participants time to consult with family members about whether or not to participate.

In conclusion, in all human research, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections (e.g., involvement of family surrogates where State or other applicable law permits and independent monitoring) may be highly advisable in certain circumstances. But treating all individuals who have cognitive deficits as incapable of understanding research is inaccurate and disrespectful of their autonomy. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs most strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

ADDENDUM: The National Bioethics Advisory Commission (NBAC) has addressed related issues and published a comprehensive report: Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. The full text of this report can be found on the NBAC web site.

The NIH Points to Consider document is generally consistent with the NBAC report, but is intended to provide practical guidance now for investigators and Institutional Review Boards (IRBs) working in these fields.

[1] Legally effective refers to informed consent as specified in 45 CFR Part 46 and to applicable state and local law and regulation.

[2] Human Subject Protection Regulations [45 CFR 46.109(b), 46.111(b) and 46.116].

[3] When some or all of the subjects are likely to be vulnerable to coercion or undue influence, including those with cognitive limitations, the IRB must be sure that additional safeguards have been included in the study to protect the rights and welfare of these subjects {45 CFR 46.111 (b); 21 CFR56.111 (b)}.