



# PROTECTING RESEARCH SUBJECTS WITH DIMINISHED CAPACITY

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The Center for Practical Bioethics' Science and Ethics Literacy Project is an initiative designed to promote informed policymaking at the state and national levels and to increase science and ethics literacy across the United States.

## BALANCING RESEARCH NEEDS WITH ETHICAL CONCERNS

By mid-century, the social and financial costs of dementia-causing conditions will be devastating, unless clinical trials can lead to ways to delay its onset, slow its progress, and possibly prevent it from occurring in our increasingly elderly population.

For research to find the near- and long-term solutions needed to help us avoid these huge costs, it must be able to study research subjects with diminished decision-making capacity. In order to promote the responsible conduct of research and to protect this population of subjects, we now must address and resolve a number of interrelated ethical and legal concerns, such as:

- Current federal regulations do not provide researchers with guidelines needed to ensure that studies involving adult subjects who have diminished decision-making capacity will be on firm ethical grounds.
- States today vary widely in their requirements for appointing surrogate decision-makers for diminished-capacity adults and in the levels of authority they give these representatives in research settings.
- Institutional Review Boards and researchers currently employ

widely differing methods for determining the degree to which someone has the capacity to provide informed consent to participate in research.

- There are no clearly defined criteria for determining the types and levels of risk to which a proposed research study could expose participating adult subjects with diminished capacity.

With a twenty-year history of building consensus on difficult issues, the Center for Practical Bioethics responded to this pressing need for policy clarity and new federal and state regulations by convening a multidisciplinary panel of national and regional experts for a day of dialogue and consensus building.

This policy brief reports the outcomes of that roundtable dialogue and presents information about the types of research needed that require involvement of adults with diminished decision-making capacity as research subjects. It also addresses the ethical issues surrounding the use of such research subjects, and makes policy recommendations intended to help shape possibly forthcoming federal regulations for protecting research subjects with diminished capacity.

## GLOSSARY OF TERMS

**Alzheimer's Disease:** a progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. Alzheimer's Disease is the most common cause of dementia.

**Assent:** an affirmative, uncoerced agreement by a potential research subject to participate in a specific research study. Mere failure to object cannot be construed as assent (see also: informed consent).

**Belmont Report:** report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) that outlines the ethical principles underlying today's regulations that guide research studies involving human subjects.

**Clinical trials:** studies of the effects of drugs, biologics, or devices upon human research subjects.

**Cognitive impairment:** impairment of intellectual functioning. Includes mild impairment, in which there is memory deficit greater than that seen in normal aging, but in which the person has essentially normal behavior in other domains.

**Common Rule:** alternative name for Subpart A of 45 CFR 46, Basic HHS Policy for the Protection of Human Subjects, which is the federal regulation that addresses protection of human research subjects.

**Dementia:** a mental state in which the symptoms of cognitive impairment are severe enough to interfere with a person's daily functioning. Dementia is not a disease, but is instead a group of symptoms that may accompany certain diseases or conditions, such as Alzheimer's Disease. Symptoms of dementia may include changes in personality, mood, and behavior.

**Informed consent:** a person's voluntary, competent agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure (see also: assent).

**Institutional Review Board (IRB):** any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. Related bodies include Central Review Boards (CRBs) and, in Canada, Research Ethics Committees (RECs).

**Legally Authorized Representative (LAR):** a person authorized either by statute or by court appointment to make decisions on behalf of another person. In human-subjects research, an individual or judicial or other body authorized under applicable law to give permission for a prospective subject to participate in a study.

**National Bioethics Advisory Commission (NBAC):** a commission whose 1998 recommendations included creating additional federal protections for a specific type of vulnerable research subject: adults with diminished decision-making capacity.

**National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research** ("the National Commission"): the commission created by the 1974 National Research Act that issued the Belmont Report.

**National Human Research Protections Advisory Committee (NHRPAC):** an advisory panel to the Office for Human Research Protections (OHRP) that issued, in 2002, recommendations concerning additional protections needed for adult research subjects with diminished capacity. NHRPAC, no longer in existence, was replaced in 2004 by the Secretary's Advisory Committee on Human Research Protections (SACHRP).

**Office for Human Research Protections (OHRP):** the Health and Human Services (HHS) office that oversees regulation of research involving human research subjects.

**Prevention studies:** Primary prevention studies are research studies designed to identify those who may be at risk for having a disease, ways to prevent people from developing the disease, or ways to prevent or delay the emergence of symptoms of the disease. Secondary prevention studies, instead, explore ways to slow the progression of the disease in those who already have it, or to prevent it from recurring in those individuals (see also: treatment studies).

**Research advance directive:** a document voluntarily prepared by an individual who anticipates that they may at some time be asked to participate in research studies, and that confirms that they still would be willing to participate, regardless of their ability to give informed consent at the time the studies are conducted.

**Research protocol:** a plan that specifies detailed procedures for a specific research study. Protocols describe the purposes and methodology of the study; the types of people who may participate in it; the schedule of tests, procedures, medications, and dosages involved; potential risks to participants; and the length of the study.

**Research proxy:** see surrogate/proxy decision maker.

**Research subject:** a person who participates in a clinical trial under the terms of a research protocol.

**Subpart D:** the portion of the current federal regulations governing research involving human subjects (45 CFR 46) that specifies special protections for children involved as such research subjects.

**Surrogate/proxy decision maker:** an individual who gives permission for an adult with cognitive impairment to participate in a research study, when that adult is not able to provide informed consent.

**Treatment studies:** research studies designed to test interventions (e.g., drugs, procedures) to examine if they can cure, reduce the symptoms of, or slow the progression of a disease, in subjects that already have it (see also: prevention studies).



## TOMORROW'S PLAGUE: THE LOOMING COSTS OF DEMENTIA-RELATED ILLNESS

Prior to the 1970s, people unlucky enough to develop age-related dementia might have been viewed with bemused exasperation, sometimes even humor. Dementia, whatever its actual cause, was at the time popularly seen as a routine feature of the aging process. Few understood that two-thirds to three-quarters of those with age-related dementias actually were victims of a severely disabling, dignity-destroying, and tragic disease: Alzheimer's. We now know, too, that like other diseases, Alzheimer's is potentially predictable, treatable, and preventable.

Until research finds effective ways to prevent and treat it, however, the longer we live, the more of us will develop age-related dementias, including dementia caused by Alzheimer's Disease. Approximately 30% of adults who live past 80 will develop Alzheimer's at some point before they die. Already, around 4.5 million Americans have Alzheimer's, and by 2050, this number is predicted to more than triple, growing to at least 13.4 million.

This coming diminished-capacity plague will have more than financial consequences. It will include serious social disruptions. Alzheimer's patients and their families already have difficulty finding, and affording, adequate nursing home and related types of

care. By mid-century, if the health care system becomes overloaded by increased numbers of Alzheimer's patients, victims of dementia who lack adequate financial and social resources will be without access to adequate care. Many of these elderly literally will be walking the streets, and our health care system will be choked with people seeking emergency dementia-related care. If this scenario is allowed to happen, our system may no longer be able to continue providing such fundamental health care and public health services as controlling cardiovascular risk factors, providing childhood immunizations, and so on.

Research must begin finding effective preventive and treatment solutions as soon as possible to help prevent this situation. Until we have the research answers needed, increasing numbers of older adults inevitably will mean higher health care and social costs. Inject into this demography-driven equation today's baby boomer bulge—Americans born between 1946 and 1964, now entering their 60's—and the costs presage a crisis. Unchecked, total U.S. medical and related social expenses of caring for Alzheimer's-related dementia will, by mid-century, reach a mind-boggling annual total of \$355 billion in today's dollars. High as it is, this figure still doesn't include costs to affected families and employers, due to such things as homecare-related expenses, lost employee wages (including the lost wages both of caretakers and of those with Alzheimer's), reduced worker productivity, and so on.

It truly will be a boon when ways are found to prevent and possibly cure Alzheimer's. But even interim solutions, including learning how to delay the onset of Alzheimer's in the elderly by a few years and slow its progress in those already diagnosed, are guaranteed to ensure significant reductions in social and financial cost.

*The consequences of Alzheimer's Disease are critically important to everybody in this room and everybody in this city and everybody in this country, because if Alzheimer's goes unchecked, those consequences will include the bankruptcy of our health care system.*

William Thies





## RESEARCH TRENDS

In 1906, when Dr. Alois Alzheimer published his first paper on the clinical and neuropathological manifestations of the disease named after him, it received little interest. Serious research into the causes and treatment of Alzheimer's began only in the mid-1970's, largely because age-related dementias, to that point, had been considered a routine aspect of growing old.

Alzheimer's Disease is by no means the whole story. It simply gives us a paradigm for the different kinds of diminished-capacity conditions that already are creating social disruption and escalating medical costs. Alzheimer's is, however, by far the most common cause of age-related dementias.

Dementia research over the past 10-15 years has reached new levels of sophistication, as reflected in the following recent shifts of research emphasis:

### **From focusing upon the mentally ill, to studying those with impaired capacity.**

Early studies did not clearly distinguish dementias and decisional incapacities due to mental illness (e.g., bipolar disorder, schizophrenia), from dementias caused by age-related, progressive diseases such as Alzheimer's.

### **From studying inpatients, to recruiting outpatients.**

Research subjects in initial Alzheimer's studies were inpatients (i.e., those already in hospitals or nursing homes). Today, studies are more likely to focus upon adults who still are living independently, or living with family members.

### **From seeking behavioral interventions, to developing medical and drug interventions as well.**

Early studies tried to find behavioral

interventions, such as helping Alzheimer's victims avoid socially inappropriate actions, sleep better, and experience less anxiety. Recent studies also are looking for drug-based treatments that may have the same benefits.

### **From looking for ways to reduce dementia symptoms, to trying also to reduce dementia itself.**

We are moving from seeking ways to treat those with diminished cognitive function and to maximize their quality of life, to looking for ways to delay the onset of the disease, and if possible, prevent it from occurring the first place.

## DIFFERENT TYPES OF STUDIES NOW ARE UNDERWAY:

### **Clinical trials.**

Scientific studies designed to help confirm whether or not specific preventive or treatment procedures, including specific drugs, are effective, and if so, whether they are effective enough.

### **Etiology studies.**

Efforts to learn, on a physical level, how Alzheimer's starts and progresses in the brain, in order to find ways to interrupt or prevent these processes.

### **Genetic studies.**

Because Alzheimer's sometimes runs in families, researchers are looking for specific risk-factor genes, i.e., genes that may indicate that someone who has such genes has a higher likelihood of developing Alzheimer's at some point in his or her life.

### **Epidemiology studies.**

Studies of this type measure the prevalence

and incidence of the disease found at different age levels and within different population groups. They also try to identify risk factors, e.g., hypertension, high cholesterol, diabetes, lack of exercise, that increase the likelihood someone will develop Alzheimer's. Of special interest are risk factors that potential victims can control by making lifestyle changes.

#### **Biomarker studies.**

These look for laboratory test results and other indicators that may be predictive of early disease. Early treatment may increase chances of delaying the disease's onset or progression.

#### **Translational studies.**

These "lab to bedside" studies investigate ways to turn basic and clinical research findings into clinical practice.

Recent findings from studies of these types suggest promising methods for diagnosing, preventing, managing the symptoms of, and slowing the progress of the disease. Topics now under investigation in research on Alzheimer's include:

- Understanding the mechanisms by which a protein called beta-amyloid forms sticky plaques in the brain. Scientists believe amyloid-based plaques may be involved in nerve cell dysfunction leading to Alzheimer's symptoms.
- Using positron emission tomography (PET) scans to spot early signs that amyloid-based plaques may be forming in the brain.
- Learning how to prevent the aggregation of beta-amyloid that may already be present in a brain, so that amyloid-based plaques do not form in the first place.
- Identifying and "turning off" specific human genes that allow peoples' brain cells to produce amyloid proteins.
- The potential of statin drugs, already widely in use to lower cholesterol levels, as a way to reduce the risk of developing Alzheimer's, or slow its progress in those who already have it.



*There has never been a time when research addressing the issue of age-related dementia has been more needed or more important. At the same time, there are concerns about whether we have the proper policy structure in place today to protect such human research subjects and to make sure they are not abused.*  
Myra Christopher



## NEEDED NOW: PARTICIPANTS FOR LARGE-SCALE RESEARCH STUDIES

**M**aking progress in dementia-related research means finding ways to delay the onset of diseases like Alzheimer's, diagnosing the presence of such diseases as early as possible, slowing their progress in those who already have them, and eventually finding ways to prevent them altogether.

But clinical research studies—those involving human rather than animal subjects or computer simulations—face complex challenges. It isn't enough simply to obtain approval to conduct a proposed clinical study or to have obtained the millions of dollars required to carry it out. In addition, clinical researchers also must successfully recruit large numbers of appropriate research subjects. In studies of the types now urgently needed, many of these subjects must be people who already have dementia.

Clinical research trials involving experimental drugs take place in three phases:

### PHASE I

This is the first stage of testing in human subjects. Such studies normally involve a small (20-80) group of healthy volunteers, however, they increasingly include persons

with specific diseases for whom all conventional therapies have failed. Phase I trials look at safety and tolerability, and at the way the body handles the drug.

### PHASE II

Once Phase I trials have confirmed that a drug or treatment is safe and tolerable in healthy people, Phase II looks at people who already have the disease or condition of interest, and also at larger groups (100-300). These trials, which often include the use of placebos, seek to determine whether the therapy in question also is effective at all, and whether it might have unforeseen, short-term, toxic side-effects.

### PHASE III

If a drug or treatment proves safe and promising once its Phase I and II studies are completed, i.e., after it has been shown to be both safe and to show promise of working as intended, Phase III trials then provide a "gold standard" for determining whether that therapy is effective enough, i.e., whether it is better than other, currently-available alternatives. Phase III studies also recruit people who already have the disease or condition, and tend to be very large (5,000-10,000 subjects). Such studies, which also often include the use of placebos, are expensive and time-consuming, especially studies testing therapies or drugs that aim at chronic conditions like Alzheimer's.

While the ethical issues apply to all three phases, key to the research process are the Phase III clinical trials. Such studies determine whether particular drugs or treatments are at least as effective as, or even more effective than, current treatment alternatives. But these Phase III trials will require many impaired-capacity research subjects.

*Every one of these four and a half million people with Alzheimer's today has a unique story. They are as unique as snowflakes. This makes it very difficult to craft public policy that spans the personal situations of all of these unique individuals.*

Linda Ward



Unlike these three-phase treatment-related studies, preventive studies, those in which researchers look for ways to help adults avoid developing dementia or to help delay its onset, instead involve recruiting apparently healthy subjects. Preventive studies planned for age-related dementias will require subjects who do not already have dementia-causing diseases or conditions such as Alzheimer's. Such preventive studies, in addition, will require even more subjects than Phase III clinical studies, upwards of 10,000 to 15,000.

For the moment, research money is flowing to Phase III trials designed to find ways of treating, rather than of preventing or curing, Alzheimer's and related dementias. Even small successes in finding effective treatments will be a step toward heading off the crushing social and financial costs of such age-related diseases.

*As the research environment, the regulatory environment, and the issues and diseases themselves all become more complicated, IRBs are going to struggle increasingly. It will be more challenging for them to understand the studies they're asked to approve, decide which of those studies pose "minimal risk" rather than "minor increases over minimal risk," agree with proposed ways for determining subjects' levels of decision-making capacity, and to work with a number of other terms that are left intentionally vague in the current regulations.*

Gary Pettett



## STUDY PARTNERS

In research settings today, subjects with diminished decision-making capacity are starting to benefit from having "study partners," people who assist those subjects during the time they are in the study.

For example, New York University's Alzheimer's Disease Center (ADC) requires each of its diminished-capacity research participants to have such a study partner. The partner must accompany the participant to his or her initial, intake-evaluation appointment and to subsequent visits, and is also expected to take part in clinical assessments.

ADC further specifies that a study partner should be someone who has regular contact with the participant, knows the participant well, and who can independently answer questions or confirm information about how the participant functions currently as compared to the past. In addition, participants should feel comfortable discussing personal information with their study partner present.

Last, ADC wants study partners to be a family member (spouse, adult child), partner, or close friend. Individuals may choose a legal guardian or someone they have designated as a health care proxy, if this person meets the other requirements.



## ETHICAL ISSUES: USING IMPAIRED-CAPACITY SUBJECTS IN RESEARCH

Under what circumstances is it appropriate to ask a person, especially one whose ability to make decisions and provide informed consent may already be limited or absent, to participate in a research study? What levels of potential, research-related risk or harm to such participants can be justified? Because vulnerable research subjects have been taken advantage of in the past, how can unethical practices be prevented in the future for dementia victims and their families?

Today, protocols for proposed clinical research studies must be approved by Institutional Research Boards (IRBs) or, in Canada, Research Ethics Committees (RECs), at the institutions where those studies are to take place. Sometimes, such studies also must be reviewed or approved by additional legally required panels before researchers can even begin recruiting human subjects into their studies. IRB reviews, shaped by current federal guidelines, are intended to protect human research subjects.

Such was not always the case. In response to revelations concerning the Public Health Service's unethical treatment of African-American men with untreated syphilis (the Tuskegee Study), Congress in 1974 initiated hearings that led to the creation of the National Commission for the Protection of Human Subjects



*I think the ultimate question for society really is, are we going to allow a third party to enroll somebody into a research situation when we know this most likely will not be for the research subject's benefit, but for somebody else's?* Scott Kim

of Biomedical and Behavioral Research. This Commission then published the Belmont Report, which outlines ethical principles that today underlie regulations guiding U.S. research studies involving vulnerable human subjects.

The landmark Belmont Report sets forth three key ethical principles:

### RESPECT FOR PERSONS

This principle addresses the need to respect the dignity and autonomy of those involved in a research study. This includes persons whose autonomy may be in question, such as persons with impaired decision-making capacity.

### BENEFICENCE

Research subjects should benefit as much as possible from the studies in which they participate, and should also be protected, as much as possible, from harm. This means maximizing any potential benefits that participation in the research may have for the subject, and minimizing any risks to which they might be exposed during the study, or afterward, as a consequence of having participated in it.

### JUSTICE

Both the risks and the benefits of a proposed research study should be fairly apportioned to those who are qualified to participate, and to those who then actually are selected, without bias or favoritism.

Following these three ethical principles, today's federal regulations protecting research subjects call for:

### INFORMED CONSENT

Based upon the ethical principle of respect for persons, anyone who agrees to participate in a research study should, to the extent they are capable of doing so, be given ample opportunity to understand what will be happening to them. They also should understand and agree to the potential risks and benefits of participating in the study before consenting to participate.

### RISK-BENEFIT ANALYSIS

Based upon the ethical principle of beneficence, researchers must analyze the potential risks and benefits their research subjects may face, and be able to explain these to potential subjects as part of the informed-consent process. Any risks to the research subject must be reasonable when compared to the anticipated benefits of the research.

*Research risk assessment is the thousand dollar issue in this field. It is all very well to be able to do capacity assessments or to identify who would be an ethical research proxy. But what it comes down to is, what is the value of what the research subject is participating in, and how does that value compare with the risks to which the subjects are being exposed?* Jason Karlawish



*Very few of our Alzheimer's patients come to us voluntarily. Instead, they come to us because they have needs. Patients are coerced in many ways by their illness, by their concerns and fears, and that's how many of our research subjects come to us as well. Although many of these subjects have altruistic concerns and motives for entering into our research protocols, most of them actually are in hopes that they are going to be helped in some way.* David Fleming



### EQUITABLE SELECTION OF RESEARCH SUBJECTS

Based upon the ethical principle of justice, researchers should select research subjects in a fair manner. They should not select subjects simply on the basis of convenience, or because the researcher personally favors certain types of individuals over others, or because they might be easy to persuade or coerce into participating.



## CURRENT REGULATIONS PROTECTING VULNERABLE RESEARCH SUBJECTS

At both federal and state levels, gaps exist in the regulations currently in place to protect vulnerable research subjects. Specifically, these gaps apply to adult, diminished-capacity research subjects. The following overview provides highlights of recent efforts to identify and provide such protections and indicates areas where increased protection and improved scientific and legal procedures still are needed.

### FEDERAL LEVEL

**NATIONAL RESEARCH ACT (1974).** Legislation passed in response to congressional investigations into the unethical treatment of human research subjects in the U.S. As part of this Act, the National Commission was created, and was charged with identifying basic ethical principles needed to protect human subjects involved in biomedical and behavioral research.

**NATIONAL COMMISSION (1978).** The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created by the National Research Act, drafted the Belmont Report, which still serves as the basis for current regulations for protecting human research subjects. The

Commission also proposed protective regulations—never adopted—intended largely to protect those “institutionalized as mentally infirm” from being abused or coerced in research situations.

**COMMON RULE (1991).** Part A of the federal regulations that were based upon the Belmont Report. This part of the regulations, originally issued by DHHS and the FDA in 1981, were in 1991 formally adopted by 17 other departments and agencies that sponsor human-subjects research, hence, they now are known as the “common rule.” These regulations currently include requirements for:

- Obtaining and documenting informed consent from research participants or from their Legally Authorized Representatives (LARs)
- Forming, running, and keeping records for Institutional Research Boards (IRBs), the panels that must review and approve research protocols for studies involving human subjects

**NBAC (1998).** The National Bioethics Advisory Commission issued guidelines for protecting the rights of an additional type of vulnerable research subject—those with diminished decision-making capacity due to mental illness. This Commission’s 21 recommendations—which have not been incorporated into federal regulations—address concerns of the following types:

- The fact that decisional capacity can change in an individual, i.e., that it can fluctuate over time
- The need to provide increased protections for diminished-capacity subjects as the potential risks involved in their participation increases and as the prospect of direct medical benefit to those patients decreases



*The prevailing practice is to allow proxy consent. Even though it goes on across the country, there’s very little actual authorization for it. Only a minority of states have legislation regarding proxy consent, and most of these laws deal with institutionalized patients. If a state’s law applies only to those who are institutionalized, does this then give you an argument for saying proxy consent is permissible for non-institutionalized patients?* David Orentlicher

- The importance of encouraging research subjects to prepare research-related advance directives
- The need to define “decisional incapacity” carefully and unambiguously

**NHRPAC (2002).** The National Human Research Protections Advisory Committee served as a multi-disciplinary advisory panel to the Office for Human Research Protections (OHRP), the federal office that oversees the regulation of human subjects research. This committee’s recommendations—again, not reflected in current federal regulations—were built upon the NBAC guidelines. Its recommendations included:

- Broadening the focus of research protections for adults who lack decisional capacity, to include those who lack such capacity for any reason rather than only for those with mental illnesses
- Clarifying, at a state level, who should be allowed to serve as a Legally Authorized Representative (LAR) (surrogate/proxy) for an adult with diminished capacity who might become involved in a research study
- The need to involve LARs during the entire time the diminished-capacity subject is recruited, involved in, and in need of withdrawing from the study

## STATE LEVEL

Because the federal common-rule regulations currently do not include protections specifically for diminished-capacity adults—protections of the types recommended in the NBAC and NHRPAC reports—states today vary widely in the legal protections they provide for such vulnerable, potential research subjects. Differences among state laws—where such laws are present at all—include:

- Inconsistencies in assigning priorities to individuals who are eligible to serve as a Legally Authorized Representative (LAR), qualified to give surrogate/proxy permission for a diminished-capacity adult to participate in a research study
- Inconsistencies in the standards that such surrogate/proxy LARS must apply in allowing a diminished-capacity adult to participate in such studies
- Inconsistencies in defining the types of risk-related studies in which diminished-capacity adults can participate
- Inconsistencies in the types of research studies in which an LAR may permit a diminished-capacity subject to participate
- Inconsistencies in criteria for confirming whether a subject has personally assented to participating



*We now see individual states moving to implement local and state regulations around who can give consent for an incapacitated individual. The longer we wait for federal guidance, the more those local and state regulations will proliferate, and the harder it is going to be to come up with something that is going to be harmonizable. This will further impair efforts to try to come up with a proxy-consent system that will actually work.* Greg Koski



## RECOMMENDATIONS: ADDITIONAL FEDERAL REGULATIONS NEEDED

Current federal regulations designed to protect the rights of research subjects involved in clinical trials do not specifically address the needs of diminished-capacity adult research subjects. To address this need, participants in the May 5, 2006, round-table meeting in Kansas City on Protection of Research Subjects with Diminished Capacity, discussed a number of additional regulations needed. On the basis of the participants' presentations and their detailed discussions, the Center for Practical Bioethics makes the following recommendations to the Office for Human Research Protections (OHRP).

### GENERAL RECOMMENDATIONS:

OHRP should add a Subpart E to the current 45 CFR 46, Protection of Human Subjects. This additional subpart might be titled "Additional Protections for Research Subjects with Diminished Cognitive Capacity." Regulations included in Subpart E should:

- 1 Be modeled after and logically consistent with the regulations in Subpart D (Children).
- 2 Incorporate, to the extent feasible, NHRPAC's recent recommendations, including its recommendation to adopt a three-level classification of research studies according to their anticipated levels of risk:

- Studies that involve no more than minimal risk to the subjects.
- Studies that include interventions or procedures that involve greater than minimal risk, but that present the prospect of direct benefit to the subjects, in which the risk is justified by the intended benefit to the subjects.
- Studies that include interventions or procedures that present a minor increase over minimal risk and do not present the prospect of direct benefit to the subjects but are likely to yield generalizable knowledge about the subject's condition or disorder.

### SPECIFIC RECOMMENDATIONS:

The new, Subpart E of the federal regulations should address the points listed under each of the following topics:

#### Confirming whether someone has "diminished capacity":

3 Provide a definition of "diminished capacity" broad enough to apply to those whose capacity is diminished for different reasons, e.g., Alzheimer's Disease, atherosclerosis-caused dementia, and brain injury. As a part of this definition, provide examples, case studies, and scenarios.

4 Avoid requiring that researchers base their assessments of "diminished capacity" upon specified procedures. Clarify that researchers must nevertheless specify the procedures they plan to use in determining whether potential study participants have required levels of diminished capacity, and document and give justification for their determinations.

5 Since consent is a continuing process, require that the decision-making capabilities of research subjects with diminished capacity be reassessed as often as is necessary.

#### Defining levels of risk a study may pose to research subjects:

6 Provide definitions, examples, and case



*Research, especially research that involves any level of risk to the subject, is not treatment; it is something fundamentally different. Under what circumstances do we allow proxies to put people into clinical trials, particularly if those trials are going to be interventional, subjecting the subject to drugs, ionizing radiation, and so on?* Karen Maschke



*One area in which the need to define “minimal risk” becomes critical is that of biomarker studies. Is having an MRI more than minimal risk? Do PET scans in which you are injected with radioactive material constitute more than minimal risk? We don’t have good definitions of the levels of risk involved in these kinds of research procedures.* Neil Buckholtz

studies that clarify what is meant by each of the different levels of risk that a proposed research study may pose. Ensure that these definitions include examples of therapeutic as well as non-therapeutic procedures that constitute each of these levels of risk.

7 In clearly defining “minimal risk” and related terms, seek public input and participation.

#### Permitting and obtaining surrogate/proxy permission:

8 Develop, and encourage states to adopt, and to allow modification by agreement among reasonably interested persons, a prioritized list of types of individuals qualified to serve as Legally Authorized Representatives (LARs) (surrogates/proxies) for individuals who may be selected as participants in research studies. Ensure that this prioritized list takes into account contemporary relationships and lifestyles, including a wide, rather than a narrow, range of individuals.

9 Require that each research participant has an advocate who stays engaged with them.

#### Confirming subject assent/dissent:

10 In keeping with Subpart D of the current regulations (protections for children), require that adult diminished-capacity subjects either assent to, or at least do not dissent from, serving as subjects in a research study. Continue to give their personal assent/dissent priority, regardless whether surrogate/proxy permission also has

been provided.

11 Include as evidence of willingness to participate in a research study, any authentic expression of the subject’s wishes, including research advance directives.

#### Review and approval of research protocols:

12 Ensure that adults who still are capable of giving informed consent, i.e., whose decision-making capacity is not sufficiently degraded, be allowed to participate in appropriate clinical studies.

13 Allow protocols for studies that involve greater than minimal risk, and that are unlikely to be of direct benefit to the participant, but that also offer the prospect of adding important scientific knowledge, and that could not otherwise be approved by an IRB, to undergo special review by HHS at the Secretary level. Such review should include public representation.

#### Federalwide Assurance:

14 Require any institution that conducts federally funded research involving adult subjects with diminished capacity to participate under the auspices of a Human Research Participant Protection Plan (HRPPP).

15 Require that studies that pose greater than minimal risk to adult subjects with diminished capacity have a Data Safety Monitoring Board (DSMB) and include methodologies to halt those studies if adverse events dictate.

*When it comes to picking research proxies, if we are going to give priority to family members,*



*we need to be as broad as possible in our definition of “family.” The person may not necessarily be someone who is a blood relative, but instead, someone who can demonstrate they have had a relationship with the person for some time, a relationship of trust.*

Kirby Randolph

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## ADDITIONAL RESOURCES

- Alzheimer's Association, Chicago, IL, <http://www.alz.org/>
- Alzheimer's Disease Research Center (ADRC), Department of Neurology, University of Washington Medical Center, St. Louis, Missouri. <http://alzheimer.wustl.edu/adrc2/>
- U.S. Dept. of Health and Human Services, Office of Human Research Protections (OHRP). <http://www.hhs.gov/ohrp/>
- U. S. National Institutes of Health, National Institute on Aging, Alzheimer's Disease Education and Referral Center (ADEAR), <http://www.nia.nih.gov/Alzheimers/>

Photos from the 2006 Roundtable Meeting: thought leaders, board members, and audience participants



Jason Karlowish and Neil Buckholtz



Beth Smith, Joan Berkley, Rosemary Flanigan



Kirby Randolph and William Theis



Dianne Shumaker and Richard Randolph



David Orentlicher, Greg Koski, Scott Kim



## THE KANSAS CITY ROUNDTABLE MEETING

The Center for Practical Bioethics' roundtable on protecting research subjects with diminished capacity was held on May 5, 2006. Participants included national and regional experts representing government, leading academic centers, advocacy groups, bioethics, the medical and legal professions, and families that have lived with dementia. The day-long session included an examination of scientific and ethical issues, a review of the historical development of current regulations, an overview of current and planned research into dementia-related illnesses, and a summary of participants' recommendations for needed, additional federal regulations.

### PARTICIPATING THOUGHT LEADERS

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## CENTER FOR PRACTICAL BIOETHICS

Founded in 1984, the Center for Practical Bioethics is an independent organization nationally recognized for its work in practical bioethics. More than a think tank, the Center puts theory into action to help people and organizations find real-world solutions to complex issues in health and healthcare.

The Center is a free-standing practical bioethics center with a vision of a society in which the dignity and health of all people are advanced through ethical discourse and action. Its mission is to raise and respond to ethical issues in health and healthcare, and its core value is respect for human dignity. The Center believes that all people have intrinsic worth, and expresses this belief by promoting both autonomy and social justice in health and healthcare.

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## THE SCIENCE AND ETHICS LITERACY PROJECT

Society is increasingly polarized over advancing technology and the ethical implications these developments present. Debates over these issues have become inflamed with uninformed rhetoric that often confounds any attempt for civil discourse to find common ground.

The Center for Practical Bioethics, in keeping with its mission of raising and responding to ethical issues in health and healthcare, launched the two-year Science and Ethics Literacy Project in early 2005. The goals of the project are to promote informed policymaking at the state level and increase science and ethics literacy across the United States.

Realizing the potential of scientific advances requires a common understanding of the issues involved and the implications and consequences of our choices. This certainly is true of the critical and growing need for studies involving Alzheimer's and other diminished-capacity research subjects. Through the Science and Ethics Literacy Project, the Center plans to create a place for communities to work together and discover both ethical and practical solutions in the life sciences that rest on the bedrock of human dignity.

The two-year project will have four phases that aim to clarify and establish the context for an informed and civil discussion of the ethics and choices involved in the life sciences and scientific research. The two initial phases of the project have involved roundtable conversations with experts from international, national, and regional perspectives, community forums, and the dissemination of policy briefs nationwide on the following initial topics:

- **Early stem cell research (Spring, 2005)**
- **Protecting research subjects with diminished capacity (Summer, 2006)**

*Editorial Committee for Issue #2: Protection of Research Subjects With Diminished Capacity*

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For more information on the **Science and Ethics Literacy Project Briefing Series** or to obtain additional copies, please contact Lorell LaBoube at 816.221.1100 or [llaboube@practicalbioethics.org](mailto:llaboube@practicalbioethics.org).

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