8. Ethical Considerations in Research: Participants with Impaired Consent Capacity

Some Governing Principles

1. The opportunity to participate in research should extend to all classes of individuals. Vulnerable populations of participants may need additional safeguards to protect their autonomy and health.
2. Participation in research must be contingent on the voluntary informed consent of the potential participant or an appropriate surrogate. Consent from the participant or surrogate, no matter how well-informed or how well it is thought to reflect the participant's interests, does not relieve the investigator and the reviewing entities from the obligation to conduct ethical research. A surrogate is someone who is empowered to authorize the participation of someone else as a subject in a research protocol. Typical surrogates include parents, adult relatives, and guardians. Occasionally, the holder of a Durable Power of Attorney for Health Care is asked to serve as a surrogate. A surrogate may exercise the noted authority only if the subject is incapable of consenting, the research poses not more than "minimal risk" to the subject, and the research is judged to be in the subject's best interests. Surrogates must avoid conflicts of interest in deciding to submit their charges to research.
3. Research protocols must be designed to take into account the special needs of individuals with ICC when developing procedures to minimize risks.
4. Research participants must not be deprived of available standard

treatments for the purposes of a research trial (e.g., given placebo arms) without adequate scientific and ethical justification. Withholding of standard, therapeutic treatments from control groups always bears a strong and distinctive burden of proof.

5. Policies that regulate human experimentation must strike an honorable balance between community and individual interests.

Discussion

Purpose

In this report, we discuss some general governing principles for research involving human participants. We are aware that additional important ethical principles may also be relevant to research. Principles governing human experimentation are the same for individuals with ICC[1] as for any research participant. However, differences may arise in implementation of those principles. These differences largely consist of additional safeguards to assure that the autonomy and health of vulnerable participants are protected. At the outset, we emphasize the heavy burden of responsibility placed on clinical investigators, research institutions, reviewing entities, and sponsors of research to protect the well-being of all participants and to merit the trust placed in them by the participants and their surrogate decision-makers.

Governing Principle 1. The opportunity to participate in research should extend to all classes of individuals. Vulnerable populations of participants may need additional safeguards to protect their autonomy and health.

VHA Mission

Mission Goal III of the *Prescription for Change*[2] is to provide excellence in education and research. The concept of excellence in VHA research encompasses active support of high quality research to stimulate and promote scientific advances that will improve clinical care and increase biomedical knowledge. VHA research is conducted within an environment that respects all participants as important partners in the process.[3] Our institutional values and principles

establish the framework for our research practices.

In VHA, the potential population of research participants includes many individuals who are among the sickest, most economically disadvantaged citizens in our nation. These veterans have made a contribution to our country through military service and many are eager to contribute again through participation in research. We must assure that opportunities to participate in research are accompanied by carefully constructed, thoughtful safeguards that make every effort to protect the health and welfare of the participants.

International Guidelines for Vulnerable Participants

"The voluntary consent of the human participant is absolutely essential."[4] Thus begins the Nuremberg Code, which remains the most rigorous standard for protection of human participants in research. The Nuremberg Code was written from the human rights perspective of war crime trial judges who were interested in protecting future research participants from abuse or harm. The rapid expansion of clinical research after World War II produced important new treatments that affected the health of communities and had significant financial impact. As the value of biomedical research to individuals and communities increased, limitations on participation and the protection of individual rights and autonomy promulgated in the Code were re-examined.

Some populations of individuals were identified who shared characteristics that made their decision to participate in research more easily influenced by factors extraneous to specific research-related issues. Other groups lacked the decision-making capacity to provide consent for themselves or to withdraw from a research protocol once they enrolled. All these groups of individuals may be included in the general category of "vulnerable."[5] If the Nuremberg Code was strictly followed, they would be excluded from participation in research because they cannot provide informed, voluntary consent for themselves.

However, these vulnerable populations of potential participants

may have a strong interest in the improvement of treatment and further understanding of the serious and often profoundly disabling disorders from which they suffer. By excluding these groups from research participation, they may be deprived of potentially beneficial treatments that are available only in the context of a research protocol. Likewise, the opportunity for research into the pathophysiology and appropriate treatments for their disorders will be irretrievably lost if these participants are never permitted to participate in research. When we consider research protocols that involve participation of vulnerable participants, we have moved beyond the human rights-based standard of Nuremberg.

In involving these participants, ethical concerns arise in appropriately balancing respect for persons and potential benefits and risks to individual research participants. Participation by these groups of individuals may also provide benefits to larger communities of patients and others in the forms of improved treatment, increased medical knowledge, and better utilization of health care resources. How to balance the rights and welfare of individuals with other societal needs raises additional difficult ethical issues.

Subsequent professional international guidelines from the World Medical Association (Declaration of Helsinki) and from the Council for International Organizations of Medical Sciences specifically permitted research in populations from whom consent could not be directly obtained or who were vulnerable.[6] Both organizations also provided recommendations for safeguards for these populations when participating in research. Although these international guidelines have no legal authority in the United States, they provide a some international perspective in discussing these issues.

U.S. Guidelines for Vulnerable Participants

In 1974, the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established to consider ethical issues in human experimentation. In 1979, the Commission issued the *Belmont Report: Ethical Principles and Guidelines*

for the Protection of Human Subjects of Research.[7] The report summarized the Commission's deliberations on the basic ethical principles underlying research involving human subjects and outlined guidelines for conducting research in accordance with those principles. The Commission also issued other reports, some of which specifically addressed concerns of involving vulnerable participants in research.[8] The reports of this Commission played an important role in providing a basis for the development of current federal regulations known as the "Common Rule."[9] These federal regulations permit research participation by certain vulnerable populations with additional safeguards, including consent from surrogates.

The Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) has published guidelines for human experimentation. These guidelines devote an entire chapter to consideration of "special classes of participants" or vulnerable populations.[10] OPRR considers vulnerable populations to be groups of individuals who, due to defects in capacity or autonomy, may not be able to give informed or voluntary consent that is consistent with their own best interests. Vulnerable populations listed in the "Common Rule" include children, prisoners, pregnant women, mentally disabled persons, and educationally or socially disadvantaged groups. Additional special classes that OPRR considers potentially vulnerable and includes in their guidelines are: traumatized and comatose patients, terminally ill patients, elderly/aged persons, minorities, students, employees, and normal volunteers.

Equitable Selection of Participants

General safeguards for participants with ICC include criteria for selection of participants that recognize concerns for justice and fairness. As a general principle, individuals with ICC shall only participate in research dealing with a condition or circumstance unique to the participant population and for which unaffected persons could not provide the information sought. If non-impaired participants would be adequate for the conduct of the research protocol, then there is no need to involve a vulnerable participant population. These

individuals cannot be considered for participation in research simply because they are conveniently located (e.g., institutionalized patients). In rare instances, however, inclusion in a research protocol may provide the only possibility of survival from a fatal disease that is unrelated to the cause of the individual's incapacity and is expected to produce death in a short period of time. The potential benefit of participating in such a protocol may justify inclusion of a participant with ICC. In such instances, and with individual approval by a reviewing body, surrogates may choose on a best interest basis to consent on behalf of the participant with ICC.

VA Patients as a Special Vulnerable Population

VA patients considered as a group may share some general characteristics with other vulnerable populations.[11] Veterans frequently come to VA because they are economically disadvantaged and are unable to afford private health care. If they are dissatisfied with their VA care, they may have no other health care option and may perceive themselves as "captive" in the VA health care system. In spite of assurances to the contrary, they or their surrogates may fear abandonment or inferior treatment if they reject an opportunity to participate in research. They may also feel a personal obligation to VA because "free" care is being provided to them and may not appreciate that they paid for their care "up front" during their military service. Other veterans, out of concern for the survival of VA in fiscally constrained times, view research protocols as a way of enhancing the reputation of VA and protecting future agency funding. Any of these issues may influence the "voluntariness" of the decision-making process.

The conduct of research in vulnerable populations requires careful consideration of ethical issues in protocol design, the consent process, and monitoring of participation.[12] This imposes special responsibilities to safeguard the participants on the investigators, institutional review boards, surrogates, sponsors, and other individuals who participate in, fund, or provide oversight for the conduct of this research. The safeguards that may be employed for vulnerable participants are discussed below in the context of the appropriate governing principle.

Governing Principle 2. Participation in research must be contingent on the voluntary informed consent of the potential participant or an appropriate surrogate. Consent from the participant or surrogate, no matter how well-informed or how well it is thought to reflect the participant's interests, does not relieve the investigator and the reviewing entities from the obligation to conduct ethical research.

General Consent Considerations

Obtaining informed consent in medical practice is a means to promote self-determination of patients by involving them in the decision-making process. This demonstrates a respect for autonomy of the individual and his/her right to exercise choice in health care. The provider may make recommendations, but he/she is bound to respect the patient's choice. This may be difficult when the provider believes the patient has made a poor choice that does not promote the patient's best interests. However, promoting and protecting a patient's well-being through beneficent action includes respecting the patient's autonomy.

An important difference between health care and research decision-making is in the nature of the choice being offered. By its very nature, research is experimental. If the benefits were known with any degree of certainty, it would not be necessary to do the experiment. The experimental nature of the undertaking makes it more difficult to weigh risks and benefits or to assess when risks are too high. Because the likelihood of benefit may be unknown or incompletely known, it also is more difficult to compare the potential value of participation in a research protocol against a standard treatment.

Full Information

The experimental nature of research participation increases the importance of providing full information to participants and the absolute requirement for the consent to be voluntary. It is standard practice to provide full detailed information in written form covering all aspects of the proposed research, including the purpose of the research, who will be involved as participants, procedures or methods,

known benefits, all possible risks, alternative options, financial considerations, and rights of the research participant. This often goes well beyond the level of detail in what would be considered a "complete" consent discussion in the clinical setting for the purposes of treatment. The practice of full disclosure is an attempt to assure that the potential participant has every possible piece of information that might be important to one in making a decision.

In obtaining consent for research participation, as in the clinical setting, stakeholders other than the patient/participant have important interests of their own. Conflicts of interest between the participant and other stakeholders can compromise the consent process. Investigators need to enroll participants in order to conduct research and may benefit either professionally or financially from the research. Research institutions benefit financially from funded research and enhance their reputation. Sponsors of the research, whether funding agencies pursuing larger societal health goals or commercial concerns trying to market a product, also have their own interests. One response to minimize the influence of these potential conflicts of interest in the consent process is to establish regulatory and oversight mechanisms. These protections afford some assurance of fully informed and voluntary consent, but they cannot guarantee it. The responsibility for respecting the autonomy of the individual ultimately lies with each investigator. We believe that a thoughtful, committed investigator who is aware of potential biases and who respects participants may be the most important means of assuring informed and voluntary consent for research.

"The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity." [13]

Voluntary Consent

Many research participants have difficulty in distinguishing between what constitutes standard treatment and what is experimental. The important subtleties of these distinctions may be

even more confusing for participants with ICC. Individuals often believe that their physician or other providers are acting in their best interest and when presented with an opportunity to participate in research often mistake this as the treatment recommendation of the provider. This may confuse their understanding of the likelihood of benefit to themselves by participation. This "therapeutic misconception" is based on their trust in the provider to do what is best for them.[14] Patients or potential participants will persist in this belief even when randomization procedures and differences in protocol arms are carefully explained. Investigators may also unwittingly confound state-of-the-art treatment with experimental treatment, particularly when standard treatments are not terribly effective. The investigator may view the research protocol as the only good "treatment option" for the patient/participant and may believe that acting beneficently means encouraging participation in the research protocol. Maintaining objectivity about the experimental nature of the protocol can be difficult for all parties involved. If objectivity is a concern, it can be partly ameliorated by having consent obtained by someone other than the participant's health care provider, if he or she is also the investigator, whenever possible.

Additional measures can be used to enhance an individual's ability to provide consent. Providing a non-stressful environment, using simple language, being receptive to questions, and responding thoughtfully in a non-hurried fashion may have significant impact on the level of a participant's understanding. A consent facilitator, either a surrogate, friend, or health care professional may provide support for the potential participant, either of a psychological nature and/or by answering questions or helping with explanations during the consent process. In some cases, a neutral consent auditor who is not acquainted with the participant and has no stake in the protocol may provide an objective third-party perspective on the individual consent process by observing the discussion and assessing whether the participant was capable of consenting, gave assent, or refused consent.[15]

Consent from Individuals with ICC

Consent for research participation must be obtained with meticulous attention to ethical considerations. Participants with ICC present special challenges.[16] These individuals have deficiencies in their abilities to reason (capacity) that will compromise their understanding of information presented. Their autonomy may be threatened by their perceptions of unequal power relationships, which, especially in institutionalized participants, may compromise the voluntary nature of their decisions. While an important concern is protecting those who are unable to give consent for themselves, investigators should be careful not to unnecessarily abridge the rights of those who can consent. A particular diagnostic category does not necessarily indicate complete compromise of decision-making capacity. Potential participants should be involved as fully as possible in the decision-making process.

To have decision-making capacity, one must be able to understand the information presented, to appreciate the consequences of acting on that information, be able to make a choice about a particular treatment or protocol, and communicate that choice. Decision-making capacity has often been described as a threshold ability (you either have it or you don't). In fact, a more useful clinical model is that of a sliding scale along a continuum of more or less risky and complicated procedures. This model is useful in ascertaining the ability of a given individual with ICC to consent to a specific research protocol. Using a sliding scale threshold, one's qualifications to give consent depend to some extent on the inherent risk of the procedure proposed and on the likelihood of direct benefit, as well as the usual criteria for decision-making capacity.[17] For example, for procedures that involve risks that may have serious, disabling, or fatal consequences, the threshold moves to a higher quality of decision-making capacity. Assessing capacity in the context of a specific research protocol may allow more participants to be involved in the decision-making process.

Determination of an individual's consent capacity is usually left up to the investigator obtaining consent. If the investigator is uncertain about the individual's ability to provide voluntary and informed consent, he/she may seek the assistance of another health professional

such as a psychiatrist, psychologist, or behavioral neurologist to assess the individual's capacity in a more detailed and complete fashion. For the purposes of informed consent for health care in VHA, when a patient is determined to lack decision-making capacity based solely on a psychiatric diagnosis (e.g., schizophrenia), then a psychiatrist must be consulted.[18] The psychiatrist must agree that the psychiatric illness has impaired the individual's capacity so severely that he/she is not capable of health care decision-making. This consultation safeguard protects individuals with a psychiatric diagnosis from being denied the opportunity to participate in decision-making when capable. Use of this type of consultative safeguard in the research setting might promote autonomous decision-making for individuals with a psychiatric diagnosis.[19]

Consent from Institutionalized Individuals

The voluntary nature of consent may be more easily compromised for institutionalized individuals. They may see consent to research as an opportunity to appear "rational" and increase their chances of an earlier discharge. They may feel emotionally dependent on caretakers and want to "please them" or be afraid of angering them and subsequently losing privileges. The opportunity afforded by a research protocol to receive extra attention or be moved to a more pleasant unit or facility may be a significant inducement to participation. Consent auditors may help provide an objective appraisal of a consent discussion. Likewise, in this group it may be especially important to have someone obtain consent who is not involved in the day-to-day care of the patient/participant or who is not in a position of authority over the participant. Another moderating influence may be the establishment of a local facility committee of institutionalized patients who review protocols to be used in the facility and who can provide patient input at the outset regarding concerns about risks or inducements.[20]

Advance Consent for Research

In some cases, it may be possible to promote participant self-determination by eliciting their wishes regarding future research participation at a time when they are capable of consenting. The NIH Clinical Center routinely utilizes a Durable Power of Attorney for Research (DPAR), which designates an authorized surrogate to give consent for participation in research. This has several advantages. It provides an opportunity for potential participants and future surrogates to explore the possible options and discuss levels of risk and benefit the potential participants might be willing to undertake. It may also allow the potential participants to discuss whether they would be willing to participate in future protocols for altruistic reasons, assuming some personal risk without any certainty or realistic possibility of direct benefit to themselves, in the hope that the knowledge obtained would benefit others. When surrogates are identified in advance, an important educational opportunity arises to explain substituted judgment and best interests decision-making and when each is appropriate, their rights as surrogates, and their responsibilities to the participants.

Another possible option is an advance directive for research or a Ulysses Contract, which is completed while the participant has capacity to consent.[21] This documents the potential participant's willingness to participate in research at a future time when he/she is no longer able to give consent. This document can be used alone or in combination with a DPAR as an indication of the participant's wishes. The Ulysses Contract must be assessed prior to participation in any specific protocol to ensure that participation is consistent with the details and qualifications of the prior consent. The Ulysses Contact should not override a participant's refusal to continue participation once research is begun.

Surrogate Consent for Research

For those individuals whose decision-making capacity is so impaired that they cannot provide consent, a surrogate decision-maker must be identified who will be responsible for making decisions on the

individual's behalf. The surrogate acts in the participant's place to make decisions and should be given any information the participant would be given, allowed to ask questions and generally treated in the same manner as the participant would have been if he or she had capacity. The best surrogates are those who know the participants well and have discussed their values and desires prior to the participants' loss of capacity. Current VHA research policy limits the list of potential surrogates and does not include other more distantly related individuals and friends who may be valuable as surrogates, particularly if they had regular and close contact with the participants.[22] If the goal in selecting surrogates is to identify the individual who is most able to represent the participants' interests, then VHA may need to reconsider who should be permitted to provide surrogate consent to research.

In addition to identifying the legally authorized surrogate, one should also consider whether that surrogate is also an ethically valid surrogate. This individual should know the participant and the participant's preferences for research participation, be willing and available to serve as surrogate, be capable of providing informed consent, and understand his or her responsibilities with regard to decision-making for the participant. When the participant's preferences are known, the surrogate is obligated to make decisions consistent with those preferences (substituted judgment). If the participant's preferences are not known, then the surrogate should attempt to utilize any clear evidence of preferences that may be available, e.g., written statements, personal conversations, knowledge of the participant's values based on a long and close relationship. If there is no available evidence to guide the surrogate, then decisions must be based on the best interests of the participant as interpreted by the surrogate. In the last circumstance, input from other friends, family members, or the personal physician of the participant may be helpful.

Fluctuating Capacity to Consent

Some research participants may have sufficient capacity to consent at the outset, but may be reasonably expected to lose capacity during the course of the research due to their underlying disorder. In this case, the investigator has an obligation at the time of enrollment to identify,

in collaboration with the participant, a surrogate who will be able to make decisions in the event that the participant loses capacity. The investigator must turn to the surrogate if the participant loses capacity during the research. The participant may further safeguard his/her interests by taking the opportunity to discuss with the surrogate his/her wishes regarding participation in the current protocol or future protocols.

Preserving the Right to Withdraw

While procedures for consent are especially labor intensive at the beginning of participation, a signature on the consent form does not end the process. In fact, the process is ongoing until participation ends. Every participant has the right to withdraw at any time from a protocol if he/she chooses to do so. Participants who lack capacity or who have fluctuating capacity may not be aware that they have the right to withdraw and a surrogate must be available to speak for them. When consent for participation has been refused or withdrawn, mechanisms must be in place to ensure that such refusal will in no way compromise or limit the access of the participants to the same quality of health care provided to those who do participate. Protection of the participants' right to self-determination ultimately falls on the investigator, who must be certain on a continuous basis that the surrogate is informed if and when the subject with varying decisional capacity loses that capacity.

Assent

Assent is "the willingness and, to the extent possible, the knowledgeable participation of those unable to give consent."[23] The investigator has an obligation to obtain the participant's assent to participation, when possible, if a surrogate provides legal consent for participation in research. Assent, like consent, is an ongoing process that includes the right to withdraw at any time. Severely impaired participants who no longer have a level of understanding sophisticated enough to provide consent for themselves are still autonomous individuals whose right to exercise self-governance, insofar as they are capable, should be respected. Assent is a safeguard to preserve the voluntary nature of participation.

Current VHA policy requires assent of the participant with ICC. "Under no circumstances may participants be forced or coerced to participate."[24] Participants who resist or who are seriously distressed by some aspect of their participation should not be forced to participate even if all other requirements for the research have been satisfied. In some situations, investigators may choose to have a consent auditor present during the discussion to confirm that the participant has indeed assented. For studies that include potential for harm or serious dislocation or discomfort, the willingness of the participants to continue should be monitored in an ongoing fashion, as an additional safeguard, by qualified professionals who are not themselves involved in the research.

In decisions regarding research participation, surrogates have not been given the authority to override an impaired participant's refusal to assent. It may be troubling, for a surrogate and others who are concerned about the participant's welfare, when a participant with ICC refuses to participate in a study that holds a possibility of providing significant benefit. Surrogates may believe that in order to fulfill their responsibilities to the participant they should be allowed to determine the relative importance to the participant of self-governance versus the likely health benefits of participation. Currently, this thorny issue has been legally resolved in favor of participant self-determination by requiring assent and not permitting surrogates to override refusals. This approach places a higher value on the autonomy and dignity of the impaired individual than health benefit and provides a limited safeguard against forcible participation of individuals with impaired capacity.

Research Participation without Consent

On October 2, 1996, the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) published amended regulations on informed consent (in the *Federal Register*). These regulations provide for an exception to the requirement that researchers obtain and document informed consent from each human participant, or his or her legally authorized representative, prior to

initiation of an experimental intervention. The exception would apply to human participants who are in need of emergency medical intervention, but who cannot give informed consent because of their life-threatening medical condition and who do not have a legally authorized person to represent them. These regulations also include requirements for consultation with representatives of the community from which the participants will be drawn, requirements for public disclosure, and the establishment of an independent data monitoring committee to exercise oversight of the research.

This action is significant because, for the first time, federal regulations permit research without the informed consent of the participant or legal representative. This action was taken after a coalition of regulators, researchers, bioethicists, and others expressed opinions in print and in a public forum sponsored by NIH and FDA. The forum considered the necessity of allowing emergency research to go forward despite the practical impossibility of requesting informed consent from participants who suddenly, because of emergency medical situations, had either significantly impaired or absent decision-making capacity. Publication of the new regulations is also significant because it signals for the first time that federal regulators recognize that rigid adherence to rules that require informed consent from participants who cannot give it (because of an emergency medical condition) may deprive participants from the chance for benefit from potentially life-saving interventions. Thus, the regulations provide that, with certain safeguards, the potential of benefit to participants may override the requirement to obtain informed consent for research.

It should be noted, however, that though there is a requirement for a community representative to provide input into the process, this is not a balancing of community interest versus individual interest. Instead, the representative is to represent the community of potential participants, i.e., individuals who might later become patients who could benefit from the proposed intervention. Thus, this regulation attempts to balance the autonomy interests of the individual with the interest of the individual to receive potentially beneficial therapy when he/she cannot consent. The fact that for the first time, with certain

safeguards, the potential of benefit to the participant may outweigh the autonomy interests of the participant may have significant implications for clinical investigations in individuals with other conditions which impair decision making capacity.

Governing Principle 3. Research protocols must be designed to take into account the special needs of individuals with ICC when developing procedures to minimize risks.

Some General Considerations

As with all research involving human participants, protocols must address a scientific or clinical question of importance and must be designed so that high quality, reproducible data may be obtained. Preliminary work in animals or model systems should be done when possible, and human participants must be essential to the project.[25] All research involving human participants should strive to minimize the risk to participants. In participant populations with ICC, there are additional criteria that should be considered. These include: 1) careful weighing of the most favorable risk/benefit ratio; 2) monitoring participants, not only for adverse effects, but also for ongoing consent capacity; 3) stopping rules that will identify participants having difficulty so they can be withdrawn by the investigator as soon as possible; 4) providing access to follow-up medical care for participants who have adverse effects and are removed from the protocol.

Evaluating Benefit and Risk

Risk may be evaluated in its relationship to potential benefits.

"Most favorable" risk/benefit ratio requires that: 1) the risk is justified by the potential direct medical benefit to the participants (i.e., the potential direct medical benefits to the individual participants outweigh the risks to those participants), and 2) the relation of the potential benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches."[26]

This rendering of the concept of risk takes into account not only the proposed procedure, but also the availability of other treatments (standard or otherwise) and considers exclusion from them as an additional possible risk. This protects the status quo of participants so that theoretically the research should not make them worse off than when they began participation. Current VHA policy is consistent with this approach.[27]

Levels of risk in human experimentation in the United States are categorized as minimal, minor increase over minimal, and greater than a minor increment over minimal risk.[28] Individuals with ICC are candidates for protocols that hold out a possibility of direct benefit, but pose only minimal risk. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that a minor increase over minimal risk also be permitted if direct benefit is expected.[29] The NIH Clinical Center and the American College of Physicians take a similar position.[30] Risks may be of a psychological, as well as physical, nature. For some participants, simply a serious disruption in daily routine may be quite stressful and may represent a significant risk to their well-being.[31]

There is much less consensus on whether individuals with ICC should ever be candidates for research that is not directly beneficial to the individual participant. The National Commission takes the position that if no direct benefit is expected, then the information sought must be of vital importance in treating the disorder and a National Review Board must be consulted. (No such board exists.) The American College of Physicians position paper takes a conservative approach that does not permit surrogates to consent for research that is greater than minimal risk and is non-therapeutic/non-beneficial to the participant. The NIH Clinical Center permits research of this type but with increased oversight and safeguards.[32] The lack of consensus among professional groups reflects the ongoing controversy in our society about how much risk an individual may undertake for the benefit of others. These concerns are summed up by Hans Jonas:

"Let us…remember that a slower process in the conquest of disease

would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, probably caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having."[33]

Minimizing Risks: Inclusion and Exclusion Criteria

Investigators are charged with minimizing risks to all research participants and additional safeguards may be needed to protect the welfare of vulnerable participants. Inclusion and exclusion criteria for enrolling participants help screen out those individuals who might be expected to have a higher risk of adverse events while enrolled in the study. These criteria may include both psychological and medical screening criteria.

Minimizing Risks: Monitoring Participation and Stopping Rules

Participants may be withdrawn from participation in a research protocol at their own or their surrogate's request or at the request of the investigator. Participants with ICC, because of their deficiencies in decision-making abilities and, in some cases, vulnerability to outside influences, may not appropriately exercise their right to withdraw. Surrogates for those who lack capacity are not always available on a daily basis, may be unaware of problems, and may have uncertainty regarding their rights and responsibilities. Careful monitoring of participants during participation in research protocols ensures that safeguards in place to protect their interests (autonomy and health) are working effectively. Monitoring is especially important to safeguard participants who may have provided consent initially, but who lose decision-making capacity during the study. Carefully crafted stopping rules developed by the investigator identify the limits of acceptable levels of adverse effects.[34] They assist in identifying individuals whose levels of risk have become unacceptable so they may be expeditiously removed from the study protocol.

Provision of Needed Medical Care to Study Dropouts

Individuals with ICC may have special difficulties in seeking and obtaining medical treatment at the appropriate time. Participants with ICC may have limited abilities to recognize the need for additional care or may have difficulty seeking care independently and may not seek it appropriately. If participants with ICC are removed from a protocol at their own request, or at the request of the investigator, because they are having difficulties beyond an acceptable level, the investigator has the responsibility to see that the participants are referred back to the appropriate health care provider. Investigators should assist participants who withdraw or are withdrawn in arranging for adequate follow-up care to assure that their continuum of care is maintained. With the permission of the participant or surrogate, any information the provider needs regarding protocol participation should be made available to them.

Governing Principle 4. Research participants must not be deprived of standard treatments for the purposes of a research trial (e.g., given placebo arms) without adequate scientific and ethical justification.

Minimizing Risk

For participants with ICC, the issues regarding risk in protocols with placebo arms are no different from those of any other class of participants. Investigators and IRBs should pay careful attention to safeguarding the welfare of all participants when they may be randomized to a placebo arm. Withholding standard treatment, no matter how ineffective or fraught with side effects that treatment is, may still pose an additional risk to participants. A number of ways to minimize risks are set out in Governing Principle 3. As in other types of protocols, participants with ICC may need additional or strengthened safeguards.

Creating a Useful Dialogue

All research participants, especially those with ICC, should be protected from unacceptable or unnecessary harms. Withholding an

available treatment from participants randomized to a placebo control arm is not always an unacceptable or unnecessary harm. The issue of the use of placebo arms rather than active controls in randomized controlled trials (RCT) has been the subject of heated discussion in the bioethics and medical literature. Those who argue that placebo arms are almost always unethical and others who do not believe that investigators should be required to justify placebo arms scientifically and ethically have taken such extreme positions that reasonable discussion and achievement of some sort of consensus becomes very difficult. These extreme positions may fail to recognize both the scientific and ethical complexities involved in the design of research trials and protection of human research participants. A more reasoned approach balancing the requirement of good science and the ethical obligations to human research participants may be necessary if we are to negotiate the complexities of this important issue successfully.[35]

It is well-established that the RCT is the best way to evaluate the efficacy (including both sensitivity and specificity) of a new therapy. The need for including placebo arms, especially in determining efficacy of treatments for disorders with a variable course and fluctuating symptomatology, has been discussed in detail elsewhere.[36] Some opponents of placebo arms assert that the motivation for their use is simply to facilitate quicker, smaller studies in order to market therapies that could be less useful than standard treatment. This generalization inaccurately represents the many possible legitimate and justifiable reasons for using placebo arms. On the other hand, there are situations in which a careful scientific re-evaluation of a proposed protocol may reveal that a placebo arm is not necessary to generate good data and thus allow research participants to continue on therapies that may be beneficial while on study.

Scientific Justification of Placebo Controls

Investigators have demonstrated that they can make thoughtful, scientifically based arguments for using placebo controls. This being the case, investigators should share that scientific justification with review boards, potential research participants, or journal editors in the same

way they would describe any other aspect of a study in a "methods" section in a publication. This is information that would be relevant to a potential participant who wants to make an informed decision. If the participant needs to consider whether to accept risks associated with discontinuing a current treatment or having a standard treatment withheld, then an explanation in layman's terms of why the investigator chose this methodology would be pertinent. The interest of a review board in approving a methodologically sound research protocol or a journal editor in publishing a report based on a well-designed protocol are also legitimate reasons for requiring a scientific justification of placebo controls.

Methodologically sound science is a necessary, but not sufficient, basis for determining whether a specific protocol meets the ethical standards for approval for human experimentation. Investigators are responsible for minimizing risks to participants. If a protocol with a placebo arm exposes participants to unnecessary or unacceptable risks, which could be avoided by a modification in the protocol design that would not render the results invalid, then the investigator is ethically obligated to make that modification. If standard therapy for a disorder is less than fully adequate (e.g., provides only symptom relief and is not curative, has limited efficacy in the patient population, is not universally better than placebo), a placebo arm is more easily justified and may be essential to demonstrate efficacy of a new therapy. A placebo arm may also be justified if current standard therapy is associated with serious side effects that are not associated with the therapy under investigation. It is almost always true that it is possible to balance the interests of science and the interests of research participants in such a way that valid research results can be obtained. More often than not, good science is good ethics.

Access to Better Therapies

One purpose of conducting clinical research is to identify new and better therapies. If an individual clearly benefits from an experimental treatment, the investigator and/or institution where the research was conducted may have an obligation to continue to provide that

treatment to the participant when they complete the study or when the study ends. Participants who were in placebo arms should also be offered the option of treatment if it may be beneficial. While it seems from an ethical point of view that a beneficial experimental treatment ought to be provided to a participant once the study ends, a number of procedural issues may make meeting this obligation very difficult. For example, if a research medication is off-formulary and very expensive, it may be difficult to shift sufficient institutional resources quickly to provide the drug to every participant who could benefit. This medication may also have to be provided in an open-label study if it has not been approved for the indication under study. As much as possible, investigators should try to work out a process in advance to assure that study participants who benefit from an experimental treatment will be able to continue on that treatment if they so desire. If it will not be possible to continue treatments that have proven beneficial while on protocol, then participants need to be given this information as part of the initial consent process.

Governing Principle 5. Policies that regulate human experimentation must strike an honorable balance between community and individual interests.

The preceding four principles derive from the philosophical tenets that autonomy of individual human beings should be respected and that the interest of vulnerable research participants should be protected. Nothing in Principle Five should be construed as minimizing the importance of these beliefs.

We acknowledge, however, that there are community interests, i.e., that the concerns and hopes of individuals in society, at present and in the future, should also be pursued. However, any consideration of research involving human participants, especially those with ICC, that focuses on future societal concerns must ensure that safeguards for individual autonomy enunciated in the four preceding principles are determinative.

For the past half century, the voluntary nature of the consent process for participation in research has been the keystone supporting

the structure of our regulatory process. As Burt has said in a recent paper about the legacy of Nuremberg: "They did not put their trust in the existence of 'civilized standards' among future professionals –neither in doctors who might consider whether to perform experiments nor in government officials who might prospectively or retrospectively judge the propriety of those experiments. The Nuremberg judges established, as their first line of defense against recurrence of these barbarities, the individual subject-patient armed with the principle of self determination. The implicit lesson that the Nuremberg judges drew from the trial testimony was that they could not place principal reliance on the self-restraining decency of traditional embodiments of social authority. This was the lesson taught not only by the doctors' trial but by the preceding war crimes trials of high government officials."[37] Our inability to account for the conduct of the Nazi experiments by well-known, respected professionals in medicine and science haunts us as we attempt to safeguard against their recurrence. In our concern for protecting individuals from the possibility of some future research enterprise run amok, we may have stifled open dialogue about the proper relationship between individuals and the community in which they live, their obligations to that community, and the relevance of community interests in research.

As other codes of research conduct have been promulgated since the Nazi Holocaust, the absolute prohibition on participation by individuals who cannot give consent has been re-examined. We routinely use surrogates to provide consent for children and those with severely impaired consent capacity. We routinely allow individuals from vulnerable groups who may not be truly capable of consenting freely to participate in research while requiring some additional (unspecified) safeguards for their welfare. Terminally ill patients regularly participate in research that offers them no direct benefit for altruistic reasons, hoping that future patients may benefit. There is recognition that some vulnerable groups of participants may or may not benefit individually from research, but that the community as a whole benefits from their participation. VHA research policy takes the conservative and widely accepted position that "incompetent people

will not be subjects of research which imposes a risk of injury unless that research is intended to benefit the subject and the probability of benefit is greater than harm."[38]

The issues of who benefits from research, balancing community and individual interests, obligations of the community to safeguard all individuals and especially vulnerable individuals, and the obligation of individuals participating in research to the larger community need to be opened for legitimate discussion. We need to assure that our research practices reflect principles that have had open, thoughtful consideration and input from all stakeholders. This requires us to step out of the shadow of Nuremberg and grapple with the complex relationships and competing priorities of individuals and their communities. If we are to protect human participants in future research, we need to explore our human values as communities as well as individuals, establish our principles for the conduct of research, and attempt to achieve some consensus on an honorable balance of our moral obligations to each other and to society.

Notes

1 Impaired consent capacity (ICC) may be defined as "the inability to provide informed consent to participate in a specific protocol. ICC is not a global assessment of a subject's cognitive status; a subject may be able to consent to one protocol, but not another." Personal communication, David Wendler, February 1996.

2 Kizer KW. *Prescription for Change*. Department of Veterans Affairs. Washington, DC, 1996.

3 This paper reviews principles that generally have relevance for all types of research involving human participants, e.g., medical, behavioral, rehabilitative, etc.

4 Nuremberg Code. *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182. Washington, DC: US Government Printing Office, 1949.

5 Robert Levine described vulnerable in this way "…those who are

relatively (or absolutely) incapable of protecting their own interests. More formally, they have insufficient power, prowess, intelligence, resources, strength or other needed attributes to protect their own interests through negotiations for informed consent," in: *Ethics and Regulation of Clinical Research*. Second Edition. New Haven: Yale University Press, 1986, p.72.

6 World Medical Association. *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and as revised by the 41st World Medical Assembly, Hong Kong, September 1989. The current CIOMS guidelines for research were reprinted without the long commentaries in "International Research Guidelines." *Bulletin of Medical Ethics* November 1993;9-11.

7 US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: US Government Printing Office, 1979.

8 US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*. Washington, DC: US Government Printing Office, 1978 and *Report and Recommendations: Research Involving Children*. Washington, DC: US Government Printing Office, 1977.

9 In June 1991, the final federal policy for protection of human subjects known as the "Common Rule" was promulgated. This common rule was developed by the interagency Human Subjects Coordinating Committee and applies to federal agencies involved in human experimentation. The "Common Rule" was published as Department of Health and Human Services 45 CFR Part 46 in the *Federal Register*; June 18, 1991;56(117):28003-28032. Vulnerable populations listed in these regulations include children, prisoners, pregnant women, mentally disabled persons, and educationally or socially disadvantaged groups.

10 US Department of Health and Human Services, National Institutes

of Health, Office for Protection from Research Risks. *Protecting Human Research Subjects: Institutional Review Board Guidebook*. Washington, DC. US Government Printing Office, 1993. Some other special classes that OPRR considers for additional safeguards, but not specifically mentioned in the "Common Rule," are: traumatized and comatose patients, terminally ill patients, elderly/aged persons, minorities, students, employees, and normal volunteers.

11 Special characteristics of patients in VHA facilities that might render them more vulnerable for the purposes of participation in research are discussed in Levine RJ, Lebacqz, K. "Some Ethical Considerations in Clinical Trials." *Clin Pharmacol Therapeutics* 1979; 25:728-741 and in McGuire, ER. "The Entitlement of Veterans Affairs Medical Patients to Vulnerable Population Status for Human Medical Research." *Health Matrix* 1992;2(259):259-301.

12 Additional guidelines for conduct of this type of research are National Alliance for the Mentally Ill. "Policies on Strengthened Standards for Protection of Individuals with Severe Mental Illnesses Who Participate as Human Subjects in Research." Arlington, VA; National Alliance for the Mentally Ill, February 14, 1995; American College of Neuropsychopharmacology. "Surrogate Consent and the Incompetent Experimental Subject," *Food Drug Cosm LJ* 46:739-771; and Berg JW. "Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines," *J of Law Med and Ethics* 1996;24:18-25. See also footnotes 15, 20, 29 and 30 in this series.

13 Nuremberg Code.

14 Therapeutic misconception is discussed in the following: DeRenzo EG. "The Ethics of Involving Psychiatrically Impaired Persons in Research." *IRB* Nov-Dec 1994;7-11; Appelbaum PS, Roth LH, Lidz C. "The Therapeutic Misconception: Informed Consent in Psychiatric Research." *International Journal of Law and Psychiatry* 1982;5:319-329; Appelbaum PS, Roth LH, et al. "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception." *Hast Cent Rep* 1987;17(2):20-4; Bamberg M,

Budwig N. "Therapeutic misconceptions: When the voices of caring and research are misconstrued as the voice of caring." *Ethics and Behavior* 2(3):165-184.

15 The notion of consent auditors has been around a long time, but they have been infrequently utilized. IRB's are permitted to send an observer at any time to evaluate the consent process. This issue is discussed further by DeRenzo in the paper cited in footnote 14 and in Keyserlinigk EW, Glass K, Kogan S, et al. "Proposed Guidelines for the Participation of Persons with Dementia as Research Subjects." *Perspectives in Medicine and Biology* 1995;38(2):319-360.

16 Some of the important issues in consent are discussed in these papers: DeRenzo E. "Surrogate Decision Making for Severely Cognitively Impaired Research Subjects: The Continuing Debate." *Cambridge Q Healthcare Ethics* 1994;3:539-548; Lane LW, Cassel CW, Bennett W. "Ethical Aspects of Research Involving Elderly Subjects: Are We Doing More Than We Say?" *J Clin Ethics* 1990;1(4):278-286; Wichman A, Sandier A. "Research Involving Subjects with Dementia and Other Cognitive Impairments: Experience at the NIH and Some Unresolved Ethical Considerations." *Neurology* 1995;45:1777-1778.

17 Drane J. "The Many Faces of Competency." *Hast Cent Rep* l985(15);17-21. The sliding scale of competence is also discussed in: Buchanan AE and Brock DW. *Deciding for Others: The Ethics of Surrogate Decision Making*. New York: Cambridge University Press, 1990.

18 VHA Handbook 1004.1, August 1, 1996, "Informed Consent."

19 Other ethical issues are discussed in Fulford KWM, Howse K. "Ethics of Research with Psychiatric Patients: Principles, Problems and the Primary Responsibilities of Researchers." *J Med Ethics* 1993;19:85-91.

[20] American College of Physicians. "Position Paper: Cognitively Impaired Subjects" *Ann of Intern Med* Nov 15, 1989;111(10):843-848.

[21] The term "Ulysses Contract" refers to the ancient Greek myth in which the ship captain Ulysses requests his crew to tie him to the mast and ignore his demands for release so that he can listen to the Siren's song without endangering himself or his ship. In the past this has referred to a document that psychiatric patients have executed consenting to anticipated future involuntary treatment. A number of useful references are provided by DeRenzo (see footnote 14) for this type of document in the clinical care setting as well as the research setting. Advance directives for research are also discussed in the American College of Physicians position paper, p. 844 (see footnote 20).

[22] VHA, M-3, Part I, Chapter 9, "Requirements for the Protection of Human Subjects." p. 9-10.

[23] *OPRR Guidebook*, p. 6-30.

[24] VHA, M-3, Part I, Chapter 9, "Requirements for the Protection of Human Subjects." p. 9-10.

[25] These guidelines are clearly set out by OPRR in the *IRB Guidebook* and international codes of conduct. A helpful resource is a detailed and thoughtful table cross-referencing a list of general, scientific, and ethical considerations for human subject research in Sutherland HJ, Meslin EM, Till JE. "What's Missing from Current Clinical Trial Guidelines? A Framework for Integrating Science, Ethics and the Community Context." *J Clin Ethics* 1994;5(4):297-302.

[26] Personal communication, David Wendler, February 1996.

[27] VHA, M-3, Part 1, Chapter 9, "Requirements for the Protection of Human Subjects" policy states, "Incompetent people will not be subjects of research which imposes a risk of injury unless that research is intended to benefit the subject and the probability of benefit is greater than the probability of harm."

[28] As defined by OPRR in the *IRB Guidebook*, p.G-8, "A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

[29] US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*. Washington, DC: US Government Printing Office, 1978 and *Report and Recommendations: Research Involving Children*. Washington, DC: US Government Printing Office, 1977.

[30] American College of Physicians. "Position Paper: Cognitively Impaired Subjects." p. 845. NIH Clinical Center. Medical Administrative Series No.87-4. "Consent Process in Research Involving Impaired Human Subjects." March 30, 1987.

[31] American College of Physicians. "Position Paper: Cognitively Impaired Subjects," p. 846.

[32] NIH Clinical Center. "Consent Process in Research Involving Impaired Human Subjects." March 30, 1987.

[33] Jonas H. "Philosophical Reflections on Experimenting with Human Subjects." *Daedalus* 1969;98:219-247.

[34] *OPRR Guidebook*, p. 3-39 through 3-41.

[35] The following references give an overview of the discussion about the use of placebos. Lasagna L. "The Helsinki Declaration: Timeless Guide or Irrelevant Anachronism?" *J Clin Psychopharm* 1995; 15(2):96-98; Tuabes G. "Use of Placebo Controls in Clinical Trials Disputed." *Science*, 1995;267:25-26; Rothman KJ, Michels KB. "The Continuing Unethical Use of Placebo Controls." *N Engl J Med* 1994;331:394-398; (A series of letters in response to the Rothman paper were published in the Jan. 5, 1995, issue of the *New England Journal of Medicine*).

[36] Leber PD. "Hazards of Inference: The Active Control Investigation." *Epilepsia* 30(suppl)1989;S57-S63; Leber PD. "Is There an Alternative to the Randomized Controlled Trial?" *Psychopharm Bull* 1991;27:3-8; De Deyn PP. "On the Ethical Acceptability of Placebo Application in Neuropsychiatric Research." *Acta Neurol Belg* 1995;(95):8-17.

[37] Burt RA. "The Suppressed Legacy of Nuremberg." *Hast Cent Rep* Sept-Oct 1996;26(5):30-33.

[38] VHA, M-3, Part 1, Chapter 9, "Requirements for the Protection of Human Subjects."

Writers

Martin L. Albert, M.D., Ph.D. - Chairperson

Arthur R. Derse, M.D., J.D.

Jane F. Joyner, R.N., J.D.

Karen J. Lomax, M.D.

Ruth Macklin, Ph.D.

Gabriel Manasse, M.D.

John Rotrosen, M.D.

Norton Spritz, M.D., J.D.