

## ETHICAL ASPECTS OF NEUROPSYCHIATRIC RESEARCH WITH HUMAN SUBJECTS

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Considerable world attention in the last century has focused on the ethics of clinical research with human subjects. Coming to the fore after World War II, with the Nuremberg War Crimes Trials, concerns were raised about the potential for abuse of nonvoluntary, uninformed subjects who might be utilized in questionable research. Out of the trials came the Nuremberg Code (1), which formalized ethical principles surrounding research with human subjects. When, in 1953, the United States opened the doors to the Clinical Center of the National Institutes of Health, guiding principles regarding human subject research at that institution were in place to greet the first subjects who enrolled in studies on site (2). By the following decade, in 1964, the World Medical Association developed the Declaration of Helsinki, which was an attempt to modify and expand upon the Nuremberg Code (1). This document classified research into clinical and nontherapeutic categories, and outlined the practice of consent that these types of research would require. The Declaration has since gone through multiple revisions and continues to be a significant guideline for research with human subjects, especially in Europe.

Despite these initial attempts to clarify the ethical principles and practices of human subject research, repeated abuses were widely publicized in the ensuing years: the Tuskegee syphilis study (3), studies involving injection of live cancerous cells in patients without their consent (4), and studies in which subjects were unknowingly exposed to radiation (5) among them. As each story was exposed, it inspired international review of the ethics of human subject research. Minority populations and those who may be vulnerable to exploitive research, such as the mentally ill, evoked particular concern. In the United States, federal commissions and agencies were created to address the concerns. Among the outcomes of these initiatives were regula-

tions affording the government greater control over federally funded research. Institutions were required to develop Institutional Review Boards (IRBs) to review research protocols to protect human subjects and ensure an adequate consent process.

Beginning in the 1990s public concern again grew, as research with patients with mental illness became a focus of media attention (6–9). As an example, Hiltz (6) in a widely publicized media report, described a study in which the use of methylphenidate in research subjects “threw 60 per cent of them into severe psychotic episodes.” Another exposé (8) described research at the University of California at Los Angeles (UCLA) involving outpatients with psychotic disorders who were withdrawn from active antipsychotic medications and observed for signs of relapse over time. One patient ultimately committed suicide more than a year after leaving the study, whereas a second had a significant exacerbation in psychotic symptoms, resulting in threats to kill his parents. In 1994 the federal Office of Protection from Research Risks (OPRR) investigated allegations that the UCLA study’s research design and implementation had been unethical (10). Although the OPRR did not find unethical research practices, they questioned the adequacy of the informed consent process for this potentially high-risk study (11).

As a result of the controversy in the United States, federal and state agencies have begun to take a closer look at ethical issues raised in psychiatric research. One of the foci has been the process of informed consent in studies involving subjects who may have impairments in their abilities to make decisions, such as patients with severe mental illnesses. A 1995 report of the Advisory Committee on Human Radiation Experiments (ACHRE) found that approximately half of the studies it examined had “inadequate explanations of risks and discomforts in their consent material and paid no attention to the question of how to deal with subjects who might have impaired capacities to consent to research participation” (5).

In 1995, President Clinton appointed the National Bioethics Advisory Commission (NBAC), in part to address these concerns. In December of 1998, NBAC issued its report entitled *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity* (12). Among other things, the report recommended that an independent professional should assess a potential subject's capacity to provide informed consent for studies involving more than minimal risk. The report generated a swift and critical response from many psychiatric professionals who expressed concern that the recommendations reflected the misconception that all persons with mental illness have decision-making impairments. Thus, some considered the recommendations too restrictive and stigmatizing of persons with illnesses very much in need of study (13). Charney (14), however, wrote on behalf of the psychiatric research community that the NBAC report provided some valuable contributions to the ongoing debate, and acknowledged that "there is a crisis in confidence in the ethics of psychiatric research" that needed to be addressed. NBAC responded to the criticisms by stating that they envisioned their report as "part of a continuing societal conversation . . . about what regulations and guidelines should govern research involving persons with mental disorders that may affect their decision-making capacity" (15).

These developments highlighted numerous areas of ethical concern regarding research with human subjects with neuropsychiatric disorders, including subject recruitment, confidentiality, data access, and conflicting roles of investigators acting also as treaters. More recently, certain methodologic practices, such as placebo-controlled studies, drug withdrawal studies, and the so-called "challenge" studies, have attracted particular attention. Related to concerns about methodology, the ability of patients with mental illnesses to provide informed consent to research procedures has probably been one of the most controversial issues surrounding psychiatric clinical research, as highlighted in the NBAC report.

## METHODOLOGIC CONTROVERSIES

### Placebo Studies

In the mid-1990s, controversy over the use of placebos in research was rekindled; some commentators (16,17) contended that placebo use is unethical when standard effective treatments exist. Support for this limitation on the use of placebos stems, in part, from the Declaration of Helsinki (1), which declares that human research subjects have a right to therapeutically proven methods and treatments when available. Nevertheless, use of placebo agents is widespread throughout medical research (18,19).

Arguments in favor of the use of placebos in research,

including psychiatric research, include the superior ability to assess accurately the efficacy of an experimental medication through the use of double-blind, randomized, placebo-controlled studies. In fact, this type of study design has been touted as "one of the major achievements of modern medicine" (20). The FDA, in considering what constitutes "adequate and well-controlled studies" (required for approval of new medications) states that the placebo-controlled experimental design has important scientific merit in establishing therapeutic efficacy as long as the objectives and the rationale for placebo use are clear (1). However, the FDA cautions that placebos should not be used "where existing treatment is life-prolonging" or if the placebo "exposes patients to a documented serious risk" (1).

Some authors have argued that findings of placebo research are misleading and deceptive (21), and that more or equally reliable findings could be had using active control agents (16,22). A central argument against the use of placebos in research on serious mental illnesses is that they are likely to contribute to a relapse of or failure to resolve psychiatric symptoms. One early report suggested that psychosis in and of itself may be biologically toxic to the brain (23), and may lead to short- and long-term adverse consequences. In addition to the potential risks associated with an exacerbation of primary symptoms, there are concerns about the psychosocial effects of relapse on patients. Specifically, prolonged periods of significant psychological distress may be associated with loss of interpersonal relationships, financial losses, and increased risk of suicide.

Despite the risks, by now it is relatively clear that the use of nonactive agents as a means of control has scientific merit when effective treatments for a particular illness are not yet known. When effective treatments do exist, a placebo comparison may still allow investigators to establish efficacy, learn more about the natural course of the illness, and compare side effect profiles of active agents against nonactive compounds. Studies examining the efficacy of a known medication and an experimental medication may—because of flaws in the studies' design or implementation—not clearly differentiate between the two, and drugs with only minimal potential may be seen as more worthwhile than they are (24). Moreover, historic controls are not an adequate substitute for placebos because the apparent increase in the prevalence of experimental subjects who may already be resistant to treatment with standard medications (25,26). Thus, the analysis of the complexities of psychiatric illness and decisions regarding the risks and benefits of existing compounds compared with novel agents would be limited by only having the existing active comparison agent as a reference point (20,27). Furthermore, it has been argued that brief placebo periods may be conducted safely, particularly for inpatients (28), and do not appear to lead to long-term negative prognostic effects (29).

## Drug Withdrawal Studies

Medication discontinuation studies in psychiatric research have become another point of ethical contention. The scientific rationale for drug discontinuation has included the desire to examine the pathophysiology and course of underlying illnesses when patients are in an unmedicated state. Furthermore, assessment of the clinical and neurochemical effects of medications in some cases can be more legitimately interpreted in a given individual after a period of drug wash-out, as the potential therapeutic or adverse effects of the initial treatment may present a confounding variable, making interpretation difficult (20,30).

However, significant concern about the use of this approach has been raised both in the scientific community and in the lay press. For example, recent literature suggests that chronic patients may have a poorer response to treatment or deleterious effects should they be taken off medication and experience relapses (31–33). In patients with bipolar disorder, concern has been raised that the clinical state following withdrawal of maintenance medication may actually be distinct from what it would have been had the natural course of the illness progressed without treatment at all (34). Furthermore, the risk of relapse itself has been of significant concern. In fact, a meta-analysis of the effects of drug discontinuation in schizophrenia demonstrated a relapse rate of 53% during an average 9.7-month follow-up (35) compared to a 16% relapse rate for those patients remaining on their medication. Despite the greater relapse risk, patients who experienced a worsening of their symptoms when off medications were able to return to baseline following reinitiation of treatment. Relapse risk may be particularly high when medications are discontinued abruptly (36,37). Questions have been raised about whether inconsistent use of neuroleptics may result in a higher risk of tardive dyskinesia (38,39).

Much as with placebos, the debate about the potential for neurotoxic damage as a result of experiencing psychosis itself (23,40) has raised further ethical questions about drug discontinuation studies. Although, the theoretic long- and short-term risks of psychosis have been widely cited, others have argued that the data on the risks of brief psychosis occurring during research studies are not clear (41,42). Furthermore, in the case of psychotic disorders, continuous treatment with neuroleptics is not without its own risks, including some risk of relapse and the risk of serious side effects (38). About 30% of patients will have no significant response to neuroleptics, and some patients can remain without relapse even after years of being off medications (43). The risks of ongoing treatment and potential adverse sequelae of withdrawing medications must be weighed in all psychiatric research. In this way, risks to human subjects may be minimized and drug withdrawal conducted when essential.

## Challenge Studies

Another of the controversial research techniques that has undergone public scrutiny are provocation or “challenge” studies. These terms refer to experiments in which patients and sometimes healthy control subjects are exposed to drugs that exacerbate or create psychiatric symptoms. Provocation studies are not unique to psychiatry. In general clinical research, provocation studies have been conducted to induce pain, nausea and/or vomiting, bronchoconstriction, tachycardia, cognitive impairment, and even sepsis (44). These studies share the same basic goal of allowing investigators to learn more about symptom expression and potential therapeutic interventions. Although widely used in medical research, their use in studies examining psychiatric illnesses seems to have captured the interest of lay persons, advocacy groups, the media, and even policy makers. One theory is that these types of studies may be more common in neurobiological research, where less is known about the diseases being studied and animal models are sparse (45).

One of the hottest debates most recently has involved the use of ketamine, an NMDA receptor antagonist, and an approved anesthetic agent, to provoke psychotic symptom exacerbation in patients with schizophrenia and produce transient psychotic states in well control subjects. Tishler and Gordon (46) expressed concern that giving a healthy control or nonpsychotic person ketamine might present a risk of producing illness, given the “biological stressor of the experimental procedure and psychological stressor of psychosis [induced by the pharmacologic challenge].” In a review of all North American schizophrenia subjects who underwent ketamine challenge studies, Carpenter (47) concluded that the ketamine-induced increase in psychosis was mild to moderate and brief, any anxiety induced was mild and brief, and there was no evidence of ongoing negative consequences for subjects. It is noteworthy, as Carpenter points out, that the controversy surrounding the ketamine challenge study has been raised when results with fewer than 50 patients have been published. The media outcry against this type of study has led to trepidation to continue this novel avenue of scientific research. Yet, other authors have suggested that symptom provocation studies, beginning with early research involving amphetamine loading and including the more recent symptom induction studies, have contributed significantly to our understanding of psychiatric disease, at a cost of inducing only transient psychotic states with no long-term adverse effects (48,49) or evidence of altered disease course (50).

Although the data suggesting the safety of current challenge studies are encouraging, ethical implementation of such studies is complex because of the potential for negative consequences, even if transient or remote. It has been argued that these types of studies might be ethically justifiable if the underlying scientific principle is sound, if the effects are

not thought to be long-term or severe, and if subjects have the capacity to participate as “knowing, voluntary partners in the research enterprise” (49).

### **INFORMED CONSENT AND THE CAPACITY FOR CONSENT IN PERSONS WITH NEUROPSYCHIATRIC DISORDERS**

Challenge, placebo, and drug withdrawal studies always raise questions of research ethics, but the controversy is heightened when the subjects involved suffer from mental illnesses. At the heart of the debate is the concern that these subjects, more than other human research subjects, have significant deficits in their abilities to provide informed consent, so that they may enter studies without full understanding of the inherent risks. Unfortunately, although this has become the focus of political and media attention, there is often a lack of understanding of what informed consent is, and what the literature shows regarding the capacity of mentally ill subjects to give informed consent.

The doctrine of informed consent is built from a complex interrelationship of medicolegal and ethical principles. Generally, informed consent, whether to research or treatment, is broken down into three parts: *voluntariness*, *disclosure*, and *competence* (51). Voluntariness implies that research subjects must be acting of their own free will when they agree to participate in research. Disclosure provides information on the basis of which potential subjects may make an informed choice. In research settings, disclosures must generally include such details as the nature and purpose of the study, as well as the potential risks and benefits involved in the study. Other information provided includes disclosure of the right to discontinue participation in the study, who will have access to the data, the differences between participation in research and routine treatment, and the availability of compensation should harm ensue as a result of the study.

Informed consent also requires task-specific competence. Competence consists of four separate elements (52). First, subjects must be able to *evidence a choice* regarding the decision at hand. The choice need not be expressed verbally, but subjects must be able to communicate their preference in some way. Also, the choice must be sustained over time. The inability to maintain a consistent choice over time might reflect significant mental status deficits such as those seen in psychotic ambivalence or delirious states.

Additionally, subjects must have a *factual understanding of the information* that has been presented to them. The degree of factual understanding required for competence is unclear, and there is no threshold value of how much information must be understood in order to be considered to have “enough” factual understanding. Furthermore, acceptable levels of understanding may vary depending on the risks involved in a proposed research study.

Subjects must also be able to *rationally manipulate the*

*information* in a way that is not impaired by symptoms of their illness. They must demonstrate ability to reason through the information presented to come up with a logical decision, which need not be the decision that the person assessing competence would make. Patients with or without psychosis who have impairments in their reasoning, in addition to their primary symptoms (e.g., cognitive deficits, concrete thinking, or inability to abstract), might have difficulties in this regard.

Finally, subjects must have a *realistic appreciation of their situation*. Patients with schizophrenia, for example, who do not believe they are ill will have a limited appreciation of why they are being enrolled in a study examining that particular illness. The appreciation must include some awareness of the fact that the study involves research and not treatment, and so may be of no direct benefit to the individual.

Understanding of the capacities of persons with mental illnesses to consent to research has historically relied on data gathered from studies looking at competence to consent to treatment. Recent years have seen an expansion of the previously limited literature on competence to consent in research settings.

With regard to the ability to communicate a choice, although sometimes taken for granted, studies have shown that a proportion of patients will have difficulties in this area. In a study by Appelbaum, Mirkin, and Bateman, 9% of community mental health center patients who were contacted to participate in a study were found to be mute or catatonic (53). Eighteen percent of primarily depressed inpatients were unable to make a decision in vignettes that required some problem solving (54). The risk of simply excluding these persons from studies is that their inability to communicate a choice may reflect a degree of illness that is worthy of study, and their exclusion might skew the results of research based on altered group composition. Therefore, there may be value in considering whether proxy decision makers might in certain circumstances and with appropriate safeguards, enter into research those subjects who are unable to express a consistent choice.

Studies have also examined the capacity of patients to understand information. For example, Grossman and Summers (55) found that patients with schizophrenia understood only about half the information presented to them regarding the risks and benefits of a fictitious medication, and thus concluded that these patients may have difficulty providing true informed consent. The degree of psychopathology may affect learning of new information in schizophrenics (56). Kleinman and colleagues (57) suggested that a formalized informing process increased schizophrenic patient understanding of tardive dyskinesia. In a frequently cited study of 41 patients with affective disorders who were potential subjects of a sleep EEG study, Roth and colleagues (58) found that only about 50% of the subjects understood more than two-thirds of the information presented to them through a formal consent process, whereas a significant mi-

nority of patients (about 25%) understood half or less of the information. Benson and associates (59) showed that patients with schizophrenia demonstrated greater impairment in understanding specific psychiatric research purposes and methodology in comparison to psychiatric patients with less severe psychopathology. Comparing the capacity of stable patients with schizophrenia and healthy volunteers to understand a low-risk study involving a magnetic resonance imaging test for research purposes, Pinals and co-workers (60) found no difference in understanding of consent forms between groups. Of note, neither group on average was able to correctly answer 100% of the questions on a brief questionnaire related to information on the consent form. Another study using a questionnaire relating to research protocols found that out of 49 patients with schizophrenia, 53% required a second trial at the questionnaire after re-education about the protocols to achieve a score of 100%, and 37% of subjects required three or more trials (61). The authors concluded that with an adequate informed consent process, research subjects with schizophrenia were able to comprehend consent form information.

Impairment of the ability to appreciate the nature of one's situation and potential consequences may have particular relevance in psychiatric disorders where insight into one's illness is often compromised. In a classic report, Soskiss (62) found that 68% of schizophrenic subjects did not recognize the reason they were receiving treatment compared to 13% of medically ill patients. In an earlier study looking at patient appreciation of their participation in research, Appelbaum and associates (63) showed that more than half of the psychiatric patients interviewed failed to comprehend the research nature of some component of the methodology of the research in which they were participating. The authors called the subjects' tendency to view research as a therapeutic process, when in fact there may be no benefit to the subject at all, the "therapeutic misconception."

With regard to the ability of psychiatric patients to rationally manipulate information pertaining to research, Stanley and colleagues (64) reported that the degree of psychopathology in patients with mental illness did not appear to influence their willingness to participate in hypothetical research compared to nonpsychiatrically ill subjects. In that study, patients tended to agree to low-risk/high-benefit hypothetical studies more than high-risk/low-benefit studies. In a subsequent study, Stanley and associates (65) found that approximately one-third of patients with mixed psychiatric diagnoses refused low-risk/high-benefit hypothetical study enrollment, whereas about 40% of patients agreed to participate in a hypothetical study of high risk/low benefit. Garety and associates (66) found that subjects with schizophrenia or delusional disorder requested less information before reaching a decision and were quicker to change their estimates of the likelihood of an adverse event compared to nondelusional psychiatric patients and normal controls. In

a study by Sachs and co-workers (67), persons with dementia were noted not to perform as well as nondemented elderly subjects in providing logical reasons for their decisions to participate in hypothetical research protocols.

Probably the most extensive data examining competency to make treatment decisions was reported by Grisso and Appelbaum (68,69) from the MacArthur Treatment Competence Study. This study utilized standardized instruments designed to assess capacities to make treatment decisions, and involved the assessment of multiple components of competence (understanding, appreciation, and reasoning) and the use of several subject groups. Deficits were most pronounced in patients with schizophrenia, and slightly more patients with depression were likely to have deficits than controls. Because the majority of all subjects performed well on measures of competence, the study underscored the notion that subjects cannot be presumed incompetent by virtue of mental illness alone.

Carpenter and associates (70) recently reported their findings examining how psychopathology and cognition affect decisional capacity. They used a modification of the MacArthur study instruments (MacCAT-CR: MacArthur Competency Assessment Tool-Clinical Research) (71) to examine making decision abilities relevant to research. In this study, 30 research subjects with schizophrenia did not perform as well as healthy controls in decision making, and performance was strongly related to cognitive impairments and somewhat related to symptomatology. However, the study found that a weeklong educational intervention that provided information regarding the hypothetical study led to improved decisional capacity such that scores of schizophrenic subjects were not significantly different from the well control group. In another recently published study, Appelbaum and associates (72) assessed the capacities of depressed patients to consent to research utilizing the MacCAT-CR. In this study, female outpatients with major depression did not show impairments in their decision-making capacities related to research. This study further demonstrated the utility of instruments such as the MacCAT-CR as a means of assessing decisional capacity as part of the broader informed consent process in an actual research study.

## COMMENTARY

Although ethics in human subject research has long been the focus of attention, awareness of the ethical dilemmas has been heightened in recent years. Despite calls for a moratorium on all nontherapeutic, "high-risk" experiments, including drug washout and challenge studies (73), adverse events appear to be much less common than the public may have been led to believe. What can be gleaned from the current debate is that researchers must attend to the concerns raised, both to maintain public trust and ensure the

ethical integrity of research itself. As Bonnie (74) noted, the challenge is to create generally accepted guidelines on safeguards for subjects without compromising the pursuit of important knowledge or threatening the integral partnership of mental health advocates, persons with mental illness, and researchers.

The research community has made several efforts to tackle these issues. The American College of Neuropsychopharmacology (ACNP) has developed guidelines on ethical practices related to neuropsychopharmacologic research. Highlighted are the needs to: (a) ensure appropriateness of the study and its design; (b) minimize risk to subjects and maximize benefit to subjects or to the population of patients with the illnesses under study; (c) ensure informed consent, while paying particular attention to the needs of those subjects who may have decision-making impairments; and (d) protect confidentiality (75). The NIMH has established new rules for “high-risk” studies, including the creation of a special Human Subject Research Workgroup of the National Advisory Mental Health Council (NAMHC), which will review study protocols involving challenge methodology or drug withdrawal studies (76). After several meetings with representatives of the NIMH, in 1995 the National Alliance for the Mentally Ill (NAMI) adopted “Policies on Strengthened Standards for Protection of Individual with Severe Mental Illnesses who Participate in Human Subjects Research” (77). Among these policies are a recognition of the “critical necessity” of human subject research, and recommendations for protection of persons with cognitive impairments, clearer standards for consent protocols, and specialized training for members of IRBs that review studies involving neuropsychiatric disorders. Measures to ensure that ethical issues are addressed have been developed, including the Research Protocol Ethics Assessment Tool (RePEAT), which may assist in the planning of experimental protocols (78).

In addition to these efforts, there is a growing consensus on mechanisms for the ethical conduct of human subject research. It has been suggested that not pursuing placebo and drug withdrawal studies would be unethical, given all there is to learn from them regarding the pathophysiology, natural course, and treatment of severe mental illness (79). That said, it also is clear that specific approaches can be utilized in order to ensure that this research is conducted safely and ethically. For example, there may be some studies of pathophysiology in which subjects may be maintained on a low but effective neuroleptic dose, without interfering with the acquisition of valid data (38). For neuroleptic withdrawal in patients with schizophrenia, slow rather than abrupt tapering with careful ongoing monitoring may mitigate potential for bad outcomes (40). Drug-free phases may best be conducted while subjects are in an inpatient setting, or while they are very closely monitored as outpatients (38). In this way, if symptoms begin to re-emerge, subjects may be quickly and effectively treated before a bad outcome ensues.

“Exit criteria” should be established *a priori* to determine when patients will be restarted on their medications (41). In addition, alternative treatments (such as adjuvant medications, psychotherapy, and rehabilitation treatments) during the placebo phase may be beneficial without compromising research design. Patients at known risk of catastrophic responses to relapse should be excluded from the subject pool. Finally, study subjects must be given the opportunity to provide informed consent, pose questions, and withdraw from study participation at any time. Those patients with initial decision-making deficits and those who may become decisionally impaired during the study will require special measures of protection, addressed in the following.

When challenge studies are proposed, again the scientific merit of the protocol must be weighed against its potential risks. Several suggestions have been made that may offer protections to subjects. For example, Tishler and Gordon (46) have suggested a careful recruitment process that would include detailed disclosure of the inherent risks, review of compensation for participation, and screening prospective normal subjects for the presence of or vulnerability to develop psychiatric illness. Miller and Rosenstein (49) indicated that: (a) the study should have clear scientific merit, (b) subjects with specific clinical vulnerabilities may need to be excluded from participation, (c) selected methods should minimize risks, (d) subjects should have access to careful monitoring and follow-up, and (e) informed consent disclosure should make clear that the challenge study is distinct from other studies in which the subject may be enrolled (80).

With regard to the consent process and the potential for decision-making impairments of mentally ill research subjects, existing literature provides only rudimentary guidance in identifying groups at high risk of impairment. A substantial number of persons with severe neuropsychiatric illnesses may have impairments in their decision-making ability related to research consent. Yet, the data also have shown that many of these persons will retain abilities to make decisions that affect their lives, and thus it is misleading to presume them incompetent by virtue of their diagnoses without adequate assessment.

Although policies will need to offer protection for those who may have decision-making impairments, excessive burdens must be avoided if advancement of knowledge is to continue. By thwarting attempts to conduct bold and novel studies, society runs the risk of limiting knowledge of the very populations who may be most in need of such research. The many subjects who have participated in neurobiological research willingly, even when the risk is high and the potential for benefit is low, testify to the desperation that some of these patients may feel regarding their illnesses. Brody has similarly commented on the justification for use of mentally infirm adults in nontherapeutic research, even if the research presents greater than minimal risk (1), because of the need

to study these complex illnesses. With these caveats, areas worthy of further consideration include disclosure practices, identification and assessment of subject competence, and questions of threshold levels of competence (81,82).

In all of these arenas, existing IRBs seem to be in a strong position to provide the scrutiny required. Unfortunately, many people believe that IRBs have become little more than clearinghouses for consent forms, rather than committees designed for careful review of all aspects of research ethics (83). In an attempt to deal with this concern, the NBAC report proposed the establishment of a special standing panel to review certain protocols that way present a greater risk to subjects (12). There are, of course, negative aspects of a shift from currently accepted local IRB authority to a federal agency far removed from where the study would take place (84). Regardless of the reviewing body, if the methodology appears questionable, persons with specialized knowledge in these areas should be consulted to address the questions raised. Attention to the minimization of potential risks of studies is also an important part of the mission of an IRB. With regard to the consent process, the IRB, in addition to reviewing consent forms, should be able to monitor investigator disclosure and determine the level of required subject competence based on a standardized evaluation of the risks and potential benefits involved in a proposed study.

Investigators may have other ways of advancing our current approaches to consent to research. For example, current literature has demonstrated that a modification of disclosure procedures may facilitate subject understanding and enhanced learning (57,59,60,70,85–89). Even with such efforts, however, there will always be potential subjects who will lack capacity, in one or more of its realms, to provide valid informed consent to participate in research. When patients are participating in studies of greater risk, a higher standard of competence should be required. The investigator and the IRB could work together to decide when formal capacity assessments are indicated (90).

After the inherent risks and competence needs are determined, a sliding scale of options regarding capacity assessment might be implemented. For example, in a low-risk study, one might consider a straightforward consent form and clinical assessment of competence, perhaps aided by a questionnaire specifically geared to the study at hand. As the stakes increase, formalized assessment instruments, such as the MacCAT-CR, might be adapted to the study in question. Oldham and colleagues (13), in their response to the NBAC report, suggested that “formal capacity assessments should be required for subjects when there is reason to believe that a mental or emotional state or a primary or secondary brain dysfunction may interfere with decision making.” They also suggest that, given the inherent potential for investigator bias, for research that presents more than a minor increase over minimal risk, independent evaluators, who function separately from the research team, could ascertain

subject capacities. It is unclear at this time how feasible such an approach would be, but it may merit exploration.

Once subjects are identified who clearly lack capacity to consent or who may come to lack capacity as research progresses (such as patients with Alzheimer’s disease or patients with schizophrenia enrolled in placebo-controlled studies), additional protections might be implemented to allow such persons to participate in research. Pursuit of a legal determination of incompetence and the appointment of a guardian to make decisions for the subject appears to be utilized rarely, in part because of the impracticalities and cost involved (51). The use of a durable power of attorney or advance directive might, however, allow a substitute decision maker to make decisions that the patient would have made during periods of greater competence (91–94).

Human subject research will always require careful scrutiny. Our history has shown that even well intentioned investigators may not be able to assess ethical aspects of the research they are undertaking objectively. Additionally, potential research subjects may enroll in studies for a variety of reasons, conscious and unconscious, without a full awareness or appreciation of the risks they are undertaking. Nevertheless, the current focus on ethical issues related to research should serve to heighten the awareness of the research team, including both investigators and subjects, regarding measures that can be taken to allow scientific advancement while protecting potentially vulnerable populations.

## ACKNOWLEDGMENT

Dr. Pinals has served on a speaker’s bureau for Janssen Pharmaceutica.

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