

Emerging Empirical Evidence on the Ethics of Schizophrenia Research

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Many challenging ethical questions come with the scientific efforts to understand the nature and treatment of schizophrenia. The empirical study of ethical aspects of schizophrenia research has sought to clarify and resolve many of these questions. In this article we provide an overview of the existing data-based literature on schizophrenia research ethics and outline directions for future inquiry. We examine 5 broad categories of inquiry into the ethics of schizophrenia research: (1) Scientific designs (eg, placebo-controlled studies and medication-free intervals, prodromal and high-risk research, and genetics research); (2) informed consent and decision-making capacity, including assessment of decisional abilities, as well as intervention studies; (3) understanding and perceptions of risk and benefit (including the therapeutic misconception); (4) influences on research participation (including voluntarism, altruism, and other motivations); and (5) key participant safeguards, such as protocol review and participant advocates. We discuss how empirical work in each of these areas answers certain questions and raises new ones. Finally, we highlight important gaps in our understanding of ethically relevant aspects of schizophrenia research and offer a specific research agenda for empirical ethics.

Key words: schizophrenia/bioethics/clinical trials/
decision-making capacity/informed consent/
empirical studies

Introduction

The personal suffering and public health consequences of schizophrenia create a societal need—many would say an ethical imperative—to perform scientific studies on its etiology, treatment, and prevention.^{1–9} The importance

of research on schizophrenia is especially great in light of the international burden of the disease.^{10–14} Moreover, current treatments, while beneficial, provide only symptomatic relief, may be difficult to tolerate, and often do not restore premorbid levels of functioning.^{15–17} In addition, many treatment approaches lack adequate empirical support.^{18–21}

Although these realities urge further research, the specific nature of this serious illness²² has raised concerns about the potential vulnerability of research participants with schizophrenia.^{5,23–25} For reasons of scientific validity,²⁶ the research needed to help those diagnosed with schizophrenia must recruit people who are actually affected by the disorder. This, in turn, has raised important questions about the ethical conduct of schizophrenia research.^{27–36} Sincere and thoughtful individuals hold different opinions on recruitment strategies, acceptable risks, appropriate safeguards, and other questions, while federal regulatory standards (such as the “Common Rule”)³⁷ do not offer specific guidance on many controversial issues.^{33,38–40} (See Fischer,⁴⁰ in this issue, for a comprehensive review of important historical documents in the field of research ethics.) The empirical study of ethical aspects of schizophrenia research has therefore sought to clarify and resolve many of these disagreements.^{32,34,41,42}

Consequently, schizophrenia research ethics has grown dramatically over the past decade, fueled by the collaborative efforts of multidisciplinary investigators, the receptiveness of editors to publish novel and early developmental work, and most important, the commitment of resources to the study of research ethics by the MacArthur Foundation, the National Institutes of Health, the National Alliance for Research on Schizophrenia and Depression, the Greenwall Foundation, the Alzheimer’s Association, and others. Prominent themes in this revitalized literature include constructive approaches to the ethical dilemmas of certain scientific designs, research participants’ strengths and vulnerabilities related to informed consent and decision-making capacity, attitudes toward clinical research and influences on research participation, protocol review, and broader considerations of scientific integrity in mental health research.^{5,24,25,43–49} In this article we provide an overview of data-based publications in schizophrenia research ethics and outline possible directions for additional inquiry.

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It is our hope that this review will help characterize the strengths and gaps in the field, inspiring future inquiry and creating a context for understanding the array of empirical and conceptual manuscripts featured in this special issue of *Schizophrenia Bulletin*.

Diverse Scientific Designs and Procedures

Diverse study designs are necessary to resolve the varied scientific questions about schizophrenia that remain. Protocols that incorporate placebo comparisons, randomization, “blinding,” and medication-free intervals help to determine the impact of pharmacologic interventions.^{50–53} Epidemiological approaches examine the association between putative etiological factors, such as infection and famine, and the later emergence of schizophrenia.^{54–57} Symptom provocation helps to examine and model illness-phenomena and their correlates.⁵⁸ Studies with people identified as “at risk” for the development of schizophrenia, such as prospective prodromal and genetic studies, help to establish biological and psychosocial vulnerabilities, sources of resilience, and other disease features.^{59,60} Such widely differing protocols require varying procedures and combinations of procedures. These may range from gathering and analyzing de-identified data from national databases to withholding medications, administering new pharmacological agents, conducting neuroimaging studies, performing in-depth structured interviews, drawing blood, or providing psychotherapy.^{61–65} Other examples exist as well, ranging from large multicenter phase 4 clinical trials to health economics and services studies, each of which differs because of the hypotheses being tested.^{66,67}

Four predominant ethics issues arise from these designs and procedures.^{29,30,68–72} First is the issue of whether novel intervention studies (especially those that are prolonged) compare new medicines with placebo, standard treatments, or “treatment as usual.”^{68,73,74} This is a particular concern in studies where standard or usual treatments offer symptomatic improvement but are of uncertain effectiveness because of imperfect prior research.³⁵ Researchers may consequently turn to placebo controls, finding it difficult to satisfy obligations to research subjects to offer “comparable” treatments, when scientific equipoise on the effectiveness of those treatments has not yet been established.^{75–77} The second issue pertains to whether the risks associated with an individual project are appropriate, eg, no single risk is excessive in proportion to the nature of the illness, the risk-benefit ratio is acceptable in light of the aims of the work, and the psychosocial and biological risks are well described.^{25,52,78,79} Objections to these kinds of risks are often raised in studies using medication-free intervals or symptom provocation.^{29,80,81} The third issue is whether sufficient safeguards protect participants from research risks.^{33,78,82} For instance, do research volunteers

truly understand the nature of the risks they are undertaking, and do institutional review board (IRB) members perform adequate oversight of more burdensome and nontherapeutic studies? Should capacity be routinely reevaluated during the course of these kinds of studies?^{83,84} Finally, are certain designs or procedures unacceptable under all or specific circumstances, perhaps for reasons related to societal values?⁶⁹ Although subjects may wish to take on certain risks, do human rights or community concerns trump their decision?^{35,85,86}

Empirical evidence has helped to address some of these ethical concerns (see Table 1). Consider, for example, the ethics of medication-free intervals and placebo comparisons in schizophrenia. Moser and colleagues recently reported on 10 patients whose antipsychotic medications were withdrawn as part of a medication washout phase.⁸⁷ Although the patients’ reasoning scores did decline, MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) Understanding and Appreciation subscale scores remained stable from before medication withdrawal until the 2-week retest (ie, still during the medication-free interval).⁸⁷ This study suggests that some participants may retain decisional abilities even when their antipsychotic medication is stopped, although further work is necessary to replicate this small study.

Roberts et al. have also provided relevant data on medication-free periods in research.^{88,89} They asked patients diagnosed with schizophrenia about the level of risk associated with a medication washout, finding that the respondents assigned “moderate risk” to this procedure. This was significantly more than having a physical examination and significantly less than a spinal tap or taking a “dangerous new medication.”⁸⁹ In this study, willingness to participate in a protocol was inversely related, and appropriate, to participants’ perceptions of study risk. It should be noted, however, that participants were given only brief descriptions of these research procedures (as opposed to a complete study consent form), and their understanding of the procedures was not assessed. Thus, more work is needed to clarify how understanding of procedures, in the context of a study as a whole, may affect perceived risks or willingness to participate.

In an earlier project, Roberts et al. had asked people with schizophrenia and psychiatrists for their views of a hypothetical clinical trial in which a study participant experienced symptom reemergence during a washout. Unexpectedly, the majority of patients and doctors recommended giving the ill study participant medication against his wishes to gain symptomatic relief and recover earlier levels of functioning.⁸⁸ This suggested a more paternalistic attitude than might otherwise be expected from these respondents.

Related concerns about medication-free intervals stem from the possibility of lasting harm from symptom

Table 1. Scientific Designs and Procedures

Theme	Article Type and <i>N</i> (if applicable)	Major Findings
Placebo-controlled studies	<ul style="list-style-type: none"> • Meta-analyses^{91,92} • Review and commentary 	<ul style="list-style-type: none"> • No conclusive evidence for higher rates of attempted or completed suicide in patients randomized to placebo vs. active drug, based on Food and Drug Administration database⁹¹ and on over 10 years of data in Netherlands.⁹² • The exclusion in most trials of patients with suicidality limits generalizability to people who would typically be eligible for these kinds of studies.⁶⁹
Medication-free intervals	<ul style="list-style-type: none"> • Survey study involving hypothetical scenario with washout phase and symptom reemergence; <i>N</i> = 59 pts with SCZ and 70 psychiatrists 	<ul style="list-style-type: none"> • Both groups rated protocol as moderately harmful, expressing low likelihood of willingness to participate (given described symptom reemergence). Most respondents (63% of pts and 52% of psychiatrists) stated view that study participant's objection to medication being given should be overridden; psychiatrists incorrectly thought that patients would be less supportive of involuntary medication in this context.⁸⁸ • See also Moser et al. 2005,⁸⁷ described in Table 2, regarding stability of decision-making abilities during medication-free period.
Views of pts regarding placebo-controls and medication washouts	<ul style="list-style-type: none"> • Survey study using hypothetical study vignettes; <i>N</i> = 59 pts with SCZ and 70 psychiatrists 	<ul style="list-style-type: none"> • Patients able to distinguish among protocols of varying levels of potential harm, viewing washout and placebo-controlled studies as having potentially more harm vs. medication trial (without placebo) or blood draw.¹²³
Understanding of placebo controls	<ul style="list-style-type: none"> • Hypothetical clinical trial consent; <i>N</i> = 49 pts with SCZ 	<ul style="list-style-type: none"> • Cognitive deficits, negative symptoms, and worse performance on MacCAT-CR Understanding and Reasoning subscales (but not general psychopathology or positive symptoms) associated with worse performance on questionnaire assessing understanding of placebos (see Dunn, Palmer, and Keehan,¹⁷¹ in this issue).
Views of genetic research	<ul style="list-style-type: none"> • Survey study; <i>N</i> = 60 employees at scientific lab and academic health center 	<ul style="list-style-type: none"> • Respondents strongly supported value of conducting genetic research on both serious mental and physical illnesses.¹¹⁵ • Respondents also viewed genetic information as more sensitive and requiring greater protection than other forms of health-related data; overall, rated as moderately likely specific negative consequences of disclosure of genetically related illness risk (eg, increased insurance expenses, uninsurability, loss of employment, diminished future work opportunities).¹¹⁶
Prodromal/first episode schizophrenia research	<ul style="list-style-type: none"> • Review articles and commentaries • Survey of relatives (<i>N</i> = 200) • Focus group (<i>N</i> = 12) • Survey of first-episode patients (<i>N</i> = 59) 	<ul style="list-style-type: none"> • Important ethical issues exist,⁹⁶ yet have received minimal empirical attention. Rates of conversion from at-risk to frank psychosis seem to vary from study to study.^{93, 95} • 85% would have visited early detection clinic earlier, 79% preferred to find out earlier.⁹⁸ • First-episode patients preferred close clinician contact, involvement in ongoing decision making.¹⁰⁰ • Side-effects, lack of social activities, male sex, and young age correlated with noncompliance during first-episode psychosis.⁹⁹

Note: Abbreviations used: MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research;¹⁴⁶ pts = patients; SCZ = schizophrenia. Unless otherwise specified, "patients" refers to patients with schizophrenia.

reemergence, although there is no conclusive evidence that harm occurs.⁹⁰ Meta-analyses of placebo-controlled studies in schizophrenia have not definitively demonstrated an increased risk of suicidality among subjects receiving placebos,^{91,92} as once feared.⁶⁸ Issues around the exclusion of suicidal patients from clinical trials are explored cogently in the article by Wilson and Stanley (in this issue).⁸⁴ Taken together, these findings underscore the need for further empirical work to respond to the concerns of participants, families, communities, clinicians, and investigators.

Similarly, empirical ethics researchers can provide more data for understanding the ethical dimensions of prodromal and first-episode schizophrenia research.^{93–96} Corcoran recently provided a comprehensive review of the ethical issues pertinent to prodromal research,⁹⁶ highlighting psychosocial risks such as stigmatization and loss of confidentiality. Additionally, the manner in which investigators define the new prodromal entities (see Wilson and Stanley,⁸⁴ in this issue) and the ways that subjects weigh the actual risks of early intervention against the potential risk of future illness remain important as well. Variation in rates of “conversion” to psychosis in clinical studies, as discussed in the article by Haroun and colleagues in this issue,⁹⁷ further complicates risk and benefit assessments. Empirical work examining the perspectives of first-episode individuals and their families,⁹³ the risks for non-compliance, and understanding of potential risks and benefits is now being conducted, while others have begun to apply the MacCAT model to capacity assessments among prodromal and first-episode subjects.^{98–101}

Currently, some of the most rapid progress in psychiatric research comes from studies that examine genetic vulnerability, interactions of genetic and environmental factors on disease expression, the role of endophenotypes, and genetic and genomic determinants of treatment response.^{102–110} However, the ethical considerations of these genetic studies have seldom been evaluated using empirical ethics methods. In a unique early study Roberts *et al.* asked people with schizophrenia their perception of risk associated with a general blood draw versus a blood draw for genetic information.⁸⁹ The respondents did not assign greater risk to the genetic test, apparently focusing solely on the minimal biological risk associated with venipuncture. This is another area where empirical ethics can be useful in describing the ethical landscape.

Specific ethical considerations for genetics research endeavors arise from the personal, social, financial, and occupational consequences (intended or not) of the quest for greater genetic information.^{111,112} What are the implications for insurability, schooling, and employment? How are people’s childbearing decisions affected? How well do people understand the complex information they receive? How much information should be provided, and what are the best educational

approaches for providing it? What protections can and should be implemented to protect private information? What are nonenrolled relatives entitled to learn? There is some preliminary evidence on the views of nonschizophrenia populations regarding genetic research, but more work is needed in schizophrenia, just as in other major neuropsychiatric illnesses.^{111,113–116}

Given the immense potential impact of genetic information, empirical ethicists cannot afford to ignore the personal, familial, societal, and policy aspects of psychiatric genetic and genomic research.^{117–119} Although investigators are currently advised not to offer research participants data from their own test results (on the grounds that the data do not meet standards for clinical utility or “reasonable medical certainty”),¹²⁰ the time will come when genetic data may be interpretable at an individual or family level. As this point nears, personal and social ethical considerations will become increasingly pressing.^{121,122}

Evidence regarding other scientific designs and procedures is lacking as well. For instance, very few studies have examined ethical issues related to different phases of multicenter clinical trials, neuroimaging, crossover designs, sequential research projects, and symptom provocation by biological interventions (eg, intravenous agents or disturbing visual images to trigger trauma-related responses and symptoms).

As we seek to understand the ethical issues associated with these designs, it will be important to assess and integrate the views of patient-participants, as well as other stakeholders, like families and clinicians. Early work comparing these perspectives has already yielded interesting and unexpected results.^{88,123} Risks associated with different kinds of research and procedures are seen differently by participants, clinicians, and different subject populations.^{88,123–125} As highlighted by the large online survey presented in this issue by Muroff and colleagues,¹²⁶ psychiatric research may be stigmatized in the eyes of the general public—in particular, the notion that people with psychiatric disorders may lack capacity to consent appeared to drive the more restrictive views of respondents toward psychiatric research compared with research on medical disorders. This important finding should raise awareness among investigators and reviewers, indicating the need to be attuned to ongoing stigma toward psychiatric research.

Finally, a relatively unexplored question concerns how best to perform ethics research itself.⁴² Issues such as what sort of threshold for capacity to consent should be required for studies on capacity to consent (see Saks, Palmer, and Dunn,¹²⁷ in this issue), the relevance of therapeutic misconception for adequacy of consent (see Miller and Wendler,⁴² in this issue), and deception in ethics-related research, for example, require further elucidation.¹²⁸

Decision-Making Capacity and Informed Consent

Descriptive Studies

An early and ongoing focus of empirical ethics work has been the assessment of decision-making capacity. It is important to note that, prior to the application of empirical methods to study consent-related abilities of people with psychiatric disorders, a common perception was that people with serious psychiatric disorders, such as schizophrenia and depression, were incompetent to consent to research.¹²⁹ In the 1980s and 1990s numerous studies began to examine this view more rigorously. (Although beyond the scope of this article to review these in detail, excellent reviews of these early studies are available.^{45,130}) In addition, investigators began to examine consent procedures themselves, suspecting that difficulties with informed consent resided at least partially in those procedures and not just in characteristics or symptoms of the patients. Intriguing results emerged from these early studies, including findings that (1) many consent forms and disclosures were inadequate, but even with improved disclosures, many patients continued to have difficulty understanding research;¹²⁹ (2) many participants in research did not understand randomization and double-blind procedures and seemed to believe that the research was conducted for their personal benefit;^{129,131,132} (3) cognitive symptoms, conceptual disorganization, and acute psychosis were related to decision-making abilities;^{133–136} and (4) patients with neuropsychiatric disorders showed both heterogeneity, as well as strengths, in informed consent contexts (relating both to research and treatment).^{134–139}

The highly innovative multiyear, multisite MacArthur competency study, which laid much of the groundwork for inquiry into decisional abilities, was the largest systematic study of capacity to consent.^{134–136} It operationalized the concepts of understanding, appreciation, reasoning, and expression of choice into semistructured interview instruments and used them to evaluate decisional abilities of people with schizophrenia or schizoaffective disorder, major depression, ischemic heart disease, and healthy control subjects matched for each diagnostic group (total $N = 498$).^{134–136} The schizophrenia and depression groups manifested worse understanding, appreciation, and reasoning compared with the control groups, and the schizophrenia subjects were more likely to score in the impaired range (defined as a level of performance that would include fewer than 5% of the community controls) compared with the patients with depression and heart disease.¹³⁵ Appelbaum et al. have since described the research strengths of subjects with moderate depression,¹⁴⁰ findings supported by Stiles et al. in their work.¹⁴¹ And as we note below (and see Table 3), people with schizophrenia show strong responses to education on the consent process.

Nonetheless, a key finding, borne out by subsequent research, was that subjects with schizophrenia showed substantial heterogeneity in their performance, and many (48%) were not impaired on any of the 3 main measures.¹³⁵ Furthermore, impairment on one scale was not predictive of impairment on the others, indicating that individuals could vary not just from one another, but also from scale to scale. Finally, test-retest findings indicated that changes in symptoms appeared to relate to changes in decisional abilities, supporting the notion that decisional abilities are not static traits but fluctuate with changes in other important factors.¹³⁴

The original instruments were lengthy and, while suited to the important and specific task of characterizing the abilities of these populations, were not subsequently adopted for more than a few other studies.^{142,143} Appelbaum and Grisso themselves—the developers of the instruments—emphasized that they were not appropriate or designed for routine clinical use.¹⁴⁴ However, the instruments were later adapted into shorter versions, evolving into the now widely used MacArthur Competence Assessment Tools for Treatment (MacCAT-T)¹⁴⁵ and Clinical Research (MacCAT-CR).¹⁴⁶

The MacArthur study was critical not only for collecting valuable data but also for highlighting the development of shared methods like well-validated assessment instruments. Numerous studies utilizing the MacCAT-T and MacCAT-CR have been conducted to date, many of which are reviewed here (also see Dunn et al.¹⁴⁷ for a review of these and other decision-making assessment tools). As with the assessment of any complex human task, however, it is unlikely that any one tool will be the ultimate authority in evaluating decision-making capacity. Thus, post-MacArthur, the continued development, refinement, and validation of tools for assessing capacity remain important for empirical ethics.^{44,147,148}

Another focus of evidence-based ethics researchers has been the effect of psychiatric symptoms on decisional abilities, particularly relative to other influences such as cognition. Early work pointed to the mixed role of psychotic symptoms in decisional impairment. For example, before, during, and after MacArthur,^{133,135,149} conceptual disorganization (as measured with the Brief Psychiatric Rating Scale¹⁵⁰) was found to be correlated with impaired understanding of treatment disclosures among schizophrenia patients. In more recent studies using the MacCAT-CR and other measures of decisional abilities, psychotic symptoms have not been as strongly or consistently associated with decisional abilities as cognitive functioning (Table 2).^{148,151–155}

Much of the recent research on decision-making capacity addresses whether, when, and to what degree people with serious mental illnesses are able to consent to research. The debate over these questions was fueled in large part by the 1998 report of the National Bioethics Advisory Commission, *Research Involving Persons With*

Table 2. Decision-Making Abilities of People With Schizophrenia and Related Disorders

Theme	Study Type and Sample <i>N</i>	Major Findings
Performance compared to other groups (healthy controls, medically ill, mentally ill)	<ul style="list-style-type: none"> ● Carpenter et al. 2000¹⁵¹: Hypothetical study; <i>N</i> = 20 inpatients and 10 outpatients with SCZ or related, and 24 controls* ● Kovnick et al. 2003¹⁵³: Hypothetical study; <i>N</i> = 27 inpatients with SCZ and 24 controls* ● Moser et al. 2002¹⁵²: Hypothetical study; <i>N</i> = 17 inpatients and 8 outpatients with SCZ and 25 HIV+ individuals ● Moser et al. 2004¹⁸⁸: Hypothetical study; <i>N</i> = 30 incarcerated mentally ill prisoners (5 with SCZ-spectrum disorders) and 30 controls ● Dunn et al. 2002¹⁶⁴: Real study (low risk); <i>N</i> = 80 outpatients with SCZ or related disorder and 19 controls ● Saks et al. 2002¹⁵⁴: Hypothetical study; <i>N</i> = 27 outpatients and 12 inpatients with SCZ or related disorder and 15 controls ● Palmer et al. 2005¹⁴⁸: Hypothetical study; <i>N</i> = 35 outpatients with SCZ, 30 outpatients with AD, and 36 outpatients with DM ● Cohen et al. 2004²²⁵: Hypothetical studies; <i>N</i> = 20 inpatients with MDD, 6 inpatients with SCZ, and 20 controls ● Combs et al. 2005²²⁶: Hypothetical study; <i>N</i> = 25 inpatients with SCZ and 25 controls ● Wirshing, Sergi, and Mintz 2005²²⁷: Real studies; <i>N</i> = 83 (SCZ) and 2 control groups: medical pts and undergraduates (<i>N</i> not provided for 2 control groups) 	<ul style="list-style-type: none"> ● Compared to healthy controls, pts had worse mean performance on MacCAT-CR (hypothetical protocol) in these 2 studies. ● Despite being sufficiently capable to consent, patients had worse mean performance on MacCAT-CR compared to the HIV+ controls. ● Mentally ill had worse mean performance on MacCAT-CR Understanding and Appreciation subscales compared to controls; on brief assessment instrument (Evaluation to Sign Consent), all but 1 had adequate capacity. ● On a 20-item post-test of comprehension, patients had lower mean scores than normal controls. ● Compared with the controls, patients had significantly lower scores on the California Scale of Appreciation, designed to assess “appreciation” component of capacity using a “false belief” operationalization. ● Despite heterogeneity within each group, on capacity instruments AD group overall had worst performance, DM pts had the best performance, and SCZ pts were intermediate. ● Controls were least impaired (based on MacCAT-CR), and were most likely to agree to participate. SCZ were the most impaired to consent and also the least likely to participate. MDD were in between controls and SCZ in both impairment and likelihood of participation. ● Without cues, SCZ pts’ recall was significantly worse than the controls; presence of cues increased their comprehension to equal the controls’ performance. ● SCZ pts < students < medical pts in initial knowledge scores regarding informed consent.
Stability of decision-making abilities	<ul style="list-style-type: none"> ● Wirshing et al. 1998¹⁵⁵: Real studies; <i>N</i> = 49 inpatients and outpatients with SCZ ● Moser et al. 2005⁸⁷: Hypothetical study; <i>N</i> = 10 pts with SCZ 	<ul style="list-style-type: none"> ● Corrected feedback until 100% correct on post-test; also 7-day retesting. At initial testing, mean score was 80% correct, with 53% requiring second trial and 37% requiring third trial to obtain 100% correct. Scores significantly improved between initial testing and 7-day retest. ● No significant changes on MacCAT-CR Understanding and Appreciation subscales during 2-week medication-free period, although Reasoning subscale scores decreased significantly.
Range of decision-making abilities	See above for details of cited studies	<ul style="list-style-type: none"> ● Heterogeneity of performance consistently found; standard deviation of pt group often greater than that of controls; also, majority of patients with SCZ not impaired on measures of decisional abilities.^{148,151,153,188}
Correlates of decision-making abilities	See above for details of cited studies	<ul style="list-style-type: none"> ● Neuropsychological measures more consistent predictor of performance on decisional abilities for research and treatment compared with measures of psychopathology.^{148,151–155,161,164,188,227,228}

Table 2. Continued

Theme	Study Type and Sample <i>N</i>	Major Findings
	<ul style="list-style-type: none"> Palmer and Jeste²²⁸ in press: 70 people with SCZ (ages 40–70) considering actual antipsychotic medication side-effects study Koren et al. 2005²²⁹: Hypothetical study; <i>N</i> = 21 inpatients with SCZ or related; focus on metacognitive vs. cognitive factors 	<ul style="list-style-type: none"> Psychopathological measures correlated in some studies: BPRS conceptual disorganization;²²⁷ BPRS overall psychopathology^{151,153} and psychosis factor;¹⁵¹ PANSS negative symptoms;^{161,171,228} and PANSS general symptomatology.²²⁸ Using comprehensive neuropsychological battery, found significant correlations between Understanding subscale of MacCAT-CR and cognition, but no specific pattern of relationships between neuropsychological domains and decisional ability areas. Metacognitive factors (ability to monitor one's performance) more strongly related to performance on MacCAT-T (especially Understanding) than direct cognitive measures (WCST)

Note: Abbreviations used: AD = Alzheimer disease; BPRS = Brief Psychiatric Rating Scale; DM = diabetes mellitus; MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research;¹⁴⁶ MacCAT-T = MacArthur Competence Assessment Tool for Treatment; MDD = major depressive disorder; PANSS = Positive and Negative Syndrome Scale; pts = patients; SCZ = schizophrenia; WCST = Wisconsin Card-Sorting Task. Unless otherwise specified, “patients” refers to patients with schizophrenia.

*Same control subjects for both studies.

*Mental Disorders That May Affect Decision-Making Capacity.*²⁸ This report, although intended to facilitate additional protections for people with mental disorders, itself became a focus of debate because it did not give adequate weight to what was already known about decisional capacity (ie, the heterogeneity of decision-making capacity among people with mental illness).^{5,130,156,157} It also seemed to single out psychiatric illness for special protections, when, in fact, many medical disorders and demographic variables (eg, lower education) appear to place people at greater risk.^{156,158,159} The report was never approved by the federal government, in part due to these concerns. Indeed, the growing body of evidence (much of which is cited here) suggests that while people with schizophrenia are more vulnerable to impaired capacity, “psychiatric patients and psychiatric research are fundamentally similar to medical patients and medical research, respectively.”^{5(p1428)} Nevertheless, the report represented a watershed event for empirical ethics research in schizophrenia. It invigorated investigators to characterize more comprehensively the decisional abilities of people with psychiatric disorders and to devise and test methods for improving the consent process.

This body of work underscores that people with schizophrenia, while at risk for impairments relative to healthy comparison groups, should not be categorically viewed as having impaired capacity because many perform as well as their non-ill counterparts. This point, as well as the heterogeneity of performance of schizophrenia patients (as evidenced by larger standard deviations on measures

of decisional abilities compared with normal comparison groups) is emphasized in the analysis provided in this issue by Jeste, Depp, and Palmer¹⁶⁰ and by Appelbaum's review.⁴⁴ As we have noted above, the collected data also indicate that cognitive impairments, rather than psychopathology, may represent the greatest threat to informed decision making.^{33,44,151,153,155,161}

Areas in need of further study related to decision-making capacity for schizophrenia research are highlighted in several other articles in this issue.^{44,162} Kim emphasizes, in a valuable conceptual piece, that translating the accumulated data on decisional abilities into categorical capacity determinations has proved challenging.¹⁶² Nevertheless, he asserts, if the field strives to inform policy-making, then this line of inquiry needs to be vigorously pursued. Given that IRBs are becoming more prone to require capacity assessments and explicit statements and justification from investigators about how capacity will be determined (as Appelbaum points out in this issue),⁴⁴ this area of research gains even more practical urgency for investigators. Other areas in need of further exploration include development and validation of brief screening tools for the identification of people at risk of impaired capacity (see, eg, Appelbaum's review in this issue),^{44,148} and investigating the ethical aspects, correlates, and complicated implications of other forms of capacity, such as financial capacity (for a thorough review of this neglected ethical topic, see Marson and Phillips,¹⁶³ in this issue).

Table 3. Intervention Studies: Informed Consent in Schizophrenia

Intervention Type	Study Type and Sample <i>N</i>	Major Findings
Feedback with multiple learning trials; cued recall	<ul style="list-style-type: none"> ● Carpenter et al. 2000¹⁵¹: Hypothetical study; <i>N</i> = 20 inpatients and 10 outpatients with SCZ or related, and 24 controls 	<ul style="list-style-type: none"> ● Pts scoring below the median of controls on MacCAT-CR Understanding subscale received multipronged educational remediation; at retesting, majority scored above cutoff; no remaining significant difference (Understanding scores) between pts and controls; Appreciation and Reasoning also improved. ● Corrected feedback until 100% correct on post-test; also 7-day retesting. At initial testing, mean score was 80% correct, with 53% requiring second trial and 37% requiring third trial to obtain 100% correct. Scores significantly improved between initial testing and 7-day retest. ● Feedback during the consent process contributed to an increased comprehension in all groups. ● Interactive questioning during the consent process did <i>not</i> lead to a significant increase in comprehension. ● Compared to non-cued recall, cues (multiple-choice recognition task) significantly improved the performance of both groups.
	<ul style="list-style-type: none"> ● Wirshing et al. 1998¹⁵⁵: Real studies; <i>N</i> = 49 inpatients and outpatients with SCZ 	
	<ul style="list-style-type: none"> ● Stiles et al. 2001¹⁴¹: Hypothetical study; <i>N</i> = 79 (SCZ), 82 (depressed), and 80 (controls) 	
	<ul style="list-style-type: none"> ● Eyler, Mirzakhanian, and Jeste 2005²³⁰: Real study (fMRI); <i>N</i> = 44 outpatients with SCZ and related ● Combs et al. 2005²²⁶: Hypothetical study; <i>N</i> = 25 inpatients with SCZ and 25 controls 	
Multimedia or video	<ul style="list-style-type: none"> ● Dunn et al. 2002¹⁶⁴: Real study (low risk); <i>N</i> = 80 outpatients with SCZ or related disorder and 19 controls 	<ul style="list-style-type: none"> ● Pts and controls in computer-enhanced consent group had greater comprehension (20-item post-test) compared to their counterparts with the routine consent; those in enhanced consent group not significantly different from controls. ● Compared videotape regarding important aspects of informed consent with a control videotape; found significantly higher understanding of consent in informed consent video group vs. control video group, overall and within each study population. ● Brief computer-based intervention (simplified) led to improved MacCAT-CR (Understanding and Appreciation) scores in SCZ group, who, postintervention, did not differ from controls on any of the 4 domains; those performing the worst at baseline showed most improvement.
	<ul style="list-style-type: none"> ● Wirshing et al. 2005²²⁷: Real studies; <i>N</i> = 83 pts with SCZ, with 2 control groups: medical patients and undergraduates (<i>N</i> not specified) 	
	<ul style="list-style-type: none"> ● Moser et al.⁸³ this issue: Hypothetical study; <i>N</i> = 30 pts with SCZ and 30 healthy controls 	

Note: Abbreviations used: fMRI = functional magnetic resonance imaging; MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research,¹⁴⁶ pts = patients; SCZ = schizophrenia. Unless otherwise specified, “patients” refers to patients with schizophrenia.

Intervention Studies

Given the findings of early decision-making studies in schizophrenia, an important next effort was to improve subject decision making. This would help optimize abilities to consent to both research and treatment. These studies (summarized in Table 3) present an encouraging picture: with thoughtful efforts aimed at providing an educational consent process, most people with schizophrenia can perform adequately on decision-making assessments. In studies using a variety of edu-

cational methods, the mean performance of patients rose to the same level as that of healthy comparison subjects.^{83,141,151,164}

Several unanswered questions remain, however. First, it is still not clear, despite numerous positive studies, what constitutes the active element of these interventions. Is it the method of education or the enriched social interaction that makes the difference in consent enhancement? Most studies did not attempt to control for this possibility (eg, with an enhanced

Table 4. Understanding/Perceptions of Research Risks and the Therapeutic Misconception

Theme	Relevant Papers and Findings
Understanding of risks	<ul style="list-style-type: none"> ● Patients ($N = 102$) had more difficulty vs. controls ($N = 20$) in identifying potential risks of enrolling in a (low-risk) real research study, although this appeared remediable with enhanced consent procedure.¹⁶⁷
Perceptions of risk/ possible harms	<ul style="list-style-type: none"> ● Pts with SCZ rated varying, hypothetical research protocols as having different levels of potential harm, and pts' ratings frequently differed from those of psychiatrists, with pts rating the vignettes as more harmful.^{88,123} ● Survey study ($N = 100$ inpatients and outpatients) reported unwillingness to participate in a placebo-controlled medication trial, primarily because of concerns about potential harms.¹⁶⁶ ● Pts with SCZ ($N = 25$) were no more likely than controls ($N = 23$) to show optimistic bias in rating likelihood of personal risks of variety of adverse events.²³¹
Therapeutic misconception	<ul style="list-style-type: none"> ● Among varied psychiatric research participants, substantial proportion manifested therapeutic misconception.¹³¹ ● Using hypothetical clinical trial protocol, found therapeutic misconception prevalent (at least 1 item of 6 answered incorrectly by two-thirds of sample ($N = 87$ pts with SCZ or SAD); degree of therapeutic misconception negatively correlated with MacCAT-CR Understanding, Appreciation, and Reasoning scores, and with cognitive functioning, yet not associated with psychopathology.¹⁸⁵ ● When questioned about reasons for participating, some respondents indicated benefit-seeking and therapeutic misconception reasoning ($N = 52$ SCZ/SAD pts).¹⁷²

Note: Abbreviations used: MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research;¹⁴⁶ pts = patients; SAD = schizoaffective disorder; SCZ = schizophrenia. Unless otherwise specified, "patients" refers to patients with schizophrenia.

social element in the control condition), nor did they generally report the comparability of time spent in each consent condition. Thus, more emphasis is needed on disentangling various aspects of the consent process.

Moreover, have any of these findings been translated into actual practice? Empirical ethics researchers must take the next step of enhancing real-world research practices. Participation on IRBs, consultation to research review systems, and insistence on the evidence-based standards now available will help assure that the valuable work conducted to date fulfills its promise of improving the ethical foundations of research. Such efforts can enhance the experiences of and protections for the volunteers who make these scientific endeavors possible.

Understanding/Perceptions of Risk and the Therapeutic Misconception

Understanding/Perceptions of Risk

All prospective research participants are expected to understand and weigh the risks of a research protocol prior to making their decision. For psychiatry researchers it is consequently important to know whether subjects understand risks adequately, whether they judge risks like nonpsychiatrically ill individuals do, and how these judgments affect their participation. There is a growing body of literature on this topic among people with schizophrenia (Table 4).

This work suggests several conclusions, as well as the need for further investigation. First, people with schizophrenia have been found to be sensitive to the special risks involved in the controversial designs described earlier. Specifically, they recognize heightened risks associated with washout and medication-free intervals.^{88,123} Moreover, patients are able to discern meaningfully among different, hypothetical research protocols of varying levels of potential harm.¹²³ In that study of decisions about washout and placebo control, patients' ratings of risk frequently differed from those of psychiatrists: patients rated the scenarios as more harmful. Roberts's team also found that willingness to participate was inversely associated with perceptions of research risks.^{88,123,165} Similarly, Hummer and colleagues indicate that concerns about potential risks associated with a placebo-controlled trial were a disincentive to participate for over half the patients surveyed.¹⁶⁶

In some cases, efforts to inform participants about the risks of specific protocols appear to need more work. For example, in a relatively low-risk protocol, researchers found that, compared with healthy controls, middle-aged and older patients with schizophrenia had more difficulty responding to an open-ended question about the potential risks of enrolling.¹⁶⁷ In this same study it was found that a computer-based, enhanced consent procedure was associated with better performance on the question.¹⁶⁷

Further studies will be needed to clarify the dimensions of nonbiological risk (eg, psychosocial, economic, anxiety-related) that are associated with taking part in

psychosocial or survey research.^{47,96,168,169} In biologically oriented research as well, the phenomenon of “respondent burden” (eg, time, energy, and emotional expenditures by participants) has received only passing interest. As defined recently by Ulrich and colleagues,^{170(p17)} “respondent burden” can be viewed as “a subjective phenomenon that describes the perception by the subject of the psychological, physical, and/or economic hardships associated with participation in the research process.” Perspectives of patients, family members, clinicians, investigators, and reviewers should be sought on the risks and burdens of existing and emerging forms of research, including “respondent burden.” Other forms of risk that have not been thoroughly elucidated have been dubbed “bystander risk”⁸⁶—namely, the biological and nonbiological risks to nonsubjects. These types of risks have been more commonly described in research on sexually transmitted diseases and genetics, but examples in psychiatric protocols have also been cited.⁸⁶ Legal, psychological, and privacy-related risks of research can also accrue to bystanders; more work is needed both conceptually and empirically to clarify the types and impact of these risks and to develop guidelines for investigators and reviewers in analyzing and safeguarding against them.

Therapeutic Misconception

Related to the focus on understanding and perception of research risks is the conceptualization of potential benefit in research. Appelbaum and colleagues have forged an intriguing line of research that seeks to uncover potential misconceptions among both participants and investigators. The foremost of these misconceptions, the inappropriate confusion or conflation of research methods and goals with those of usual clinical care, has been termed “the therapeutic misconception.”¹³¹ This misconception leads to an unrealistic or inappropriate expectation of personal benefit or individualized care. A number of authors in this issue discuss the relevance of the therapeutic misconception to the ethical basis of schizophrenia research.^{42,171–173}

Since the initial description of the therapeutic misconception in 1982,¹³¹ investigators and commentators have been concerned and puzzled about this problematic—and possibly quite prevalent—aspect of research participation.¹⁷⁴ Although the initial misconception studies involved patients who were participating in psychiatric research, the phenomenon has since been described in many nonpsychiatric research populations.^{175–180} The true prevalence and risk factors for therapeutic misconception remain elusive, however, in part because consensus has not yet emerged on what beliefs or statements truly constitute it.¹⁸¹ Moreover, whether evidence of therapeutic misconception should invalidate informed consent or invoke extra protections also requires clarification.^{42,182}

Several relevant studies have now been completed, although more work is needed to identify specific vulnerabilities and to develop interventions designed to address them. Ideally, future studies will use shared methods (including validated measures of the therapeutic misconception and its effects), allowing results to be compared meaningfully.

Among those studies already completed, the largest investigated the therapeutic misconception in a wide variety of research protocols. Lidz, Appelbaum, and colleagues¹⁸³ employed extensive interviews with 225 subjects enrolling in 44 research trials (ranging from phase 1 cancer chemotherapy trials to other phase 3 and 4 trials). They examined beliefs about research participation, risks and benefits, and differences between research and usual care. Nearly a third of research participants appeared to hold inaccurate beliefs regarding the degree of individualization of their treatment (termed “TM₁”). Approximately one-half of participants held unreasonable beliefs regarding the nature or likelihood of benefit (deemed unreasonable based on the specific study in which they were enrolling and called “TM₂”). Over 60% of participants manifested a therapeutic misconception judging by one or both of these criteria.^{183,184} Older age, lower education, and worse self-described health placed people at risk for holding a therapeutic misconception.

In a study of people with schizophrenia, Dunn and colleagues used a brief, 6-item questionnaire asking about TM₁-related beliefs within a hypothetical, placebo-controlled, clinical trial.¹⁸⁵ Of 87 patients with schizophrenia or schizoaffective disorder, approximately two-thirds answered at least 1 question incorrectly. However, nearly one-third answered all items correctly, suggesting that many participants are able to distinguish the sometimes subtle differences of research from usual care.

Performance on this particular measure of therapeutic misconception was correlated with MacCAT-CR performance and with neuropsychological functioning, but not with psychopathology. In Candilis and colleagues’ report (in this issue), the authors also found that some respondents did not seem to grasp the inherent uncertainty of the scientific method, believing that they would “get a better treatment.”¹⁷² However, differentiating the therapeutic misconception from hope and trust in one’s doctor remains an elusive yet necessary aspect of ethics research.

In a semistructured interview study of people with schizophrenia, Roberts *et al.* have found that respondents consistently indicate that research of varying kinds offers greater benefit “to society” than to individual participants (unpublished data). This suggests that some schizophrenia research volunteers may indeed have an intellectual understanding of the overall goals of research. A cautionary note, however, is that participants in this study erroneously ascribed benefit to individual study volunteers enrolled in “toxicity” studies, indicating

that people with schizophrenia may not understand all types of protocols without specific consent processes to support their understanding.

These findings all point to the need, expressed for a number of years, for brief, targeted efforts to address the therapeutic misconception. Educating research participants about key distinctions between research and usual care are essential to these efforts.^{132,174} Because these distinctions will depend on the unique characteristics of a given protocol, efforts should be made to develop educational interventions tailored to specific types of studies (eg, pharmacologic, psychosocial, genetic).

Influences on Research Participation

Voluntarism

Informed consent encompasses not only the provision of relevant information and the presence of decision-making capacity but also voluntariness.¹⁸⁶ As articulated in *The Belmont Report*, voluntariness in research participation “requires conditions free of coercion and undue influence.”¹⁸⁶ Operationalizing these broad requirements has proved more challenging. Compared to the conceptual and empirical work on information disclosure and decision-making capacity, voluntarism has received relatively little attention until recently (Table 5).^{187,188}

Like other concerns about psychiatric research, those related to voluntarism arise from worries about the abilities of people with mental illness to exercise their autonomy. Can subjects identify and enact their genuine preferences in the face of serious symptoms and difficult life circumstances? Some fear that these challenges—though not unique to psychiatric syndromes—may lead to increased vulnerability or perceptions of pressure to participate. These concerns have not been adequately investigated using empirical methods.^{187,189,190}

Several recent articles have attempted to address this void in more detail. Roberts, for example, offered a conceptual model of voluntarism¹⁸⁹ that employs a positive operationalization. In this view, voluntarism may comprise 4 components—including authenticity based in one’s own circumstances, history, clarity, intentionality, and coherence with one’s values. Roberts’s outline of 4 domains that contribute to voluntarism (developmental; illness-related; psychological, cultural, and religious; and external features and pressures) provides a starting point for inquiry: which elements, for example, affect the decision about whether to participate, and which affect the entire experience of participation?

Nelson and Merz parsed voluntariness slightly differently (although the same fundamental domains articulated by Roberts are apparent in their model).^{187,189} Their model describes potential influences on voluntariness arising from the characteristics of research subjects,

including capacity, socioeconomic factors, and other role- or illness-related factors. It also details potential researcher- and setting-related factors. These include 3 forms of influence initially described by Faden and Beauchamp, ie, persuasion, manipulation, and coercion.¹⁹¹ As Nelson and Merz emphasize, our knowledge of the prevalence of any of these influences is limited because of the paucity of research.

In research examining the genetics of psychiatric disorders, voluntarism takes on a previously unstudied dimension—the effect of family and its role. Families can affect participation decisions, ongoing study involvement, and poststudy information sharing.¹⁹² These aspects of voluntarism (which seem to fall into several of the domains outlined by Roberts) have also not been studied adequately. Work in other fields (notably the genetics of breast cancer and Huntington’s disease)^{193–195} can be informative, but it is not necessarily descriptive of the experience of persons with mental illness.

Motivations for Participation in Research

People with schizophrenia report several positive motivations for their decisions to enroll in research projects. Similar to other research populations, patients with schizophrenia endorse the scientific, social, psychological, and compensation-related benefits of participation.^{165,196} A series of semistructured interview studies by Roberts et al. have documented that people with schizophrenia express altruistic attitudes pertaining to research. They seek to help society, to help science, to help others with the illness (now and in the future), and to help foster hope.^{196,197} People with schizophrenia cite a number of other factors that influence their reasons for participating in research.^{165,196,198–200} For instance, approximately half of a sample of participants with schizophrenia who were interviewed in depth about their motivations cited biological need.¹⁶⁵

Although limited data exist regarding the differences between individuals who do and do not agree to participate in research—in part, because it is difficult to conduct these kinds of studies—the data that do exist tend to support the notion that patients with schizophrenia are fundamentally similar to patients with medical illnesses.^{172,198,199,201,202} For example, Candilis and colleagues’ novel work on this issue indicates that patients with schizophrenia and schizoaffective disorder provide a combination of socially directed and personally motivated reasons for research participation. Because this hypothetical study related to an antibiotic trial, rather than a trial of antipsychotic medication, it would be interesting to learn more about motivations for participation decisions related specifically to psychiatric trials, particularly as risks escalate.

There is also little data examining the role of financial incentives to participate in research. For years, concerns

Table 5. Influences on Research Participation

Theme	Relevant Papers and Findings
Conceptual models of voluntarism	<ul style="list-style-type: none"> • 4-domain model: (1) developmental factors; (2) illness-related considerations; (3) psychological issues and cultural and religious values; and (4) external features and pressures.¹⁸⁹ • Model includes participant, researcher, and research context-related factors;¹⁸⁷ relies on Faden and Beauchamp's description of continuum of possible influences, ranging from persuasion, to manipulation, to coercion,¹⁹¹ combined with potential vulnerability of research participants.
Coercion	<ul style="list-style-type: none"> • Among 30 incarcerated mentally ill patients (5 with SCZ-spectrum disorders), susceptibility to coercion (as measured by Iowa Coercion Questionnaire, instrument under development) was higher in those with worse neuropsychological functioning, but evidence of <i>actual</i> coercion not found.¹⁸⁸
Views of research benefits to society and to self; trust in researchers	<ul style="list-style-type: none"> • Patients rate societal benefits of research as higher than personal benefits (structured interviews, $N = 59$).¹²³ • Psychiatrists accurately gauged patients' personal motives for participating, while underestimating patients' altruistic motives.¹⁹⁶ • Among 28 patients currently enrolled in a research protocol, majority reported trusting the person who told them about the protocol; most felt the decision was easy to make.²³²
Altruistic and personal motivations for participation in research	<ul style="list-style-type: none"> • Individuals with SCZ endorsed the scientific importance of research on SCZ and of autonomy in decision making. Psychiatrists underestimated role of hope and of family, physician, and investigator influences on patients' decision making about research participation.¹⁹⁷ • Qualitative (interview) data examining view of trial participants with SCZ; approximately half of those participating in actual protocol cited "biological need" (eg, current medications not working) as major reason for participating. Frequent motivating factors included psychological/social benefits (eg, ability to help others) and rewards (eg, financial compensation).¹⁶⁵ • Patients ($N = 59$) generally agreed that an offer of financial compensation would make them more likely to agree to participate in hypothetical medication trial involving washout phase;⁸⁸ also generally viewed monetary incentives as having a mild influence on decisions, along with physician recommendations about participation.¹²³ • Among incarcerated mentally ill ($N = 30$), main motivations for participating in hypothetical study were to alleviate boredom, to gain opportunity for socialization, and to help others.¹⁸⁸ • Altruism more frequently given as reason for participation by patients who were willing to participate in hypothetical trial vs. by those who were unwilling (unwilling subjects were more likely to express general aversion to research) (see Candilis et al.¹⁷² in this issue). Other frequently mentioned considerations were treatment-related benefits, as well as potential risks, but neither of these categories of reasons differed significantly between willing vs. unwilling respondents; monetary compensation infrequently mentioned.¹⁷²
Correlates of willingness to participate	<ul style="list-style-type: none"> • Willingness to participate negatively associated with level of perceived risks various study designs.^{46,123,233} • Male inpatients ($N = 155$) asked to participate in "low-risk" research (no financial compensation offered): younger patients and those diagnosed with SCZ were more likely to participate.²⁰¹ • Patients with SCZ ($N = 6$) less likely to agree to participate in variety of research studies compared with patients with MDD ($N = 20$), who were less likely than controls ($N = 20$); psychiatric participants no more likely than controls to agree to participate in riskier study.²²⁵ • Among 52 patients, greater willingness to participate in hypothetical antibiotic clinical trial was associated with higher education, higher MacCAT-CR Understanding and Choice subscale scores, higher MMSE scores, and lower total PANSS and lower General psychopathology scores (see Candilis et al.¹⁷² in this issue).

Note: Abbreviations used = MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research;¹⁴⁶ MDD = major depressive disorder; MMSE = Mini-Mental State Examination; PANSS = Positive and Negative Symptoms Scale; SCZ = schizophrenia. Unless otherwise specified, "patients" refers to patients with schizophrenia.

have been expressed about the potentially coercive effects of monetary payments, although others have tried to allay these concerns.^{203–207} Yet the few empirical studies that have been conducted (in nonpsychiatric patients)

do not clearly indicate that monetary payments lead potential research subjects to ignore risk.^{202,208} Similarly, Candilis et al. found that the role of monetary compensation for a hypothetical antibiotic trial seemed to be

minimal for most participants.¹⁷² By contrast, Roberts et al. found that monetary compensation was given greater weight than doctors' and family recommendations by people who were considering hypothetical medication-free and placebo-control schizophrenia protocols.^{88,123} These findings point to the need for further study of how potential participants balance various influences. Studying the effects of financial and other types of compensation, in combination with and relative to other potential influences on decision making in actual, not just hypothetical, research contexts, would be particularly valuable.¹⁹⁰

Gaining a better understanding of the motivations and barriers to research participation is valuable for all clinical research. Scientific implications fuel this area of empirical ethics research as well, as enrollment of nonrepresentative samples is a threat to external validity.²⁶ In view of such concerns, Halpern has proposed a novel method for eliciting the views and preferences of potential enrollees.²⁰⁹ This method, called "prospective preference assessment," involves polling potential participants (eligible for a planned trial) prior to the formal recruitment process. Barriers to recruitment could be identified and the design modified if indicated. Differences between those who would or would not enroll could also be assessed. This strategy, which can be adapted to schizophrenia research, could easily be evaluated for its effect on efficiency of recruitment and enrollment and on the composition of resulting participant pools.

Key Safeguards: Protocol Review and Participant Advocates

Human research employs many safeguards, some of which—like informed consent, conflict of interest management, confidentiality protections, and institutional review board oversight—are federally regulated. Others—like scientific review processes, debriefing methods, and publication processes—are not. Most of these topics, with the exception of informed consent, have received relatively little attention in empirical studies. As a result, little is known; much remains to be explored. Protocol review by IRBs, ongoing protocol monitoring, and participant debriefing are less scrutinized dimensions of schizophrenia research (Table 6). Because these have a strong influence on the design and conduct of protocols, it is problematic that we do not know more about how they occur and how they affect the research experiences of participants. (The commentary provided in this issue by Shore reflects the need for greater exploration of such issues as participant debriefing, the use of sliding scale risk-benefit assessments, and the use of consent monitors.¹⁷³)

The IRB review process, while critical to any study, is itself not well understood or characterized. Only a few studies have been conducted examining the work of

IRBs, with most data coming from general descriptions of IRB members or analysis of consent forms and applications.^{210–212} Data on the risk-benefit assessments or other review criteria used by IRB members are far less plentiful.^{213,214} Despite the ongoing discussions about risk, and the need to protect potentially "vulnerable" groups, minimal data exist about how IRBs actually arrive at their complex decisions.^{215,216} IRBs take on the extraordinary challenge of reviewing myriad protocols involving patients with medical and neuropsychiatric disorders, yet there is almost no guidance about how to define terms such as "vulnerability,"³³ how to determine whether investigators have provided protections adequate to the risks of a study, and how to identify adequate group decision making.

Recently, Shah and colleagues at the National Institutes of Health Department of Clinical Bioethics identified variable risk assessments among IRB chairs reviewing pediatric protocols—assessments whose interpretation of risk often ran counter to "available data on risks and [federal] regulations themselves."^{217(p476)} Others have described the variability among IRBs when they assess the benefits of clinical research.²¹⁸

For psychiatry in particular, there are many unanswered questions: how do review board members assess risks of psychiatric protocols as opposed to those from other specialties? What factors (eg, protocol-related, reviewer-related, investigator-related) influence the process and outcome of these reviews? Does the review process itself differ for psychiatric and nonpsychiatric protocols, and if so, in what ways? Does variability in interpretation of federal standards affect the assignment of protections to psychiatric subjects?

A large landmark survey of IRB members, chairs, and investigators at 491 IRBs did not explicitly examine differences in level or effectiveness of oversight among different types of protocols (eg, for psychiatric versus medical protocols). The findings, published in 1998 and known as the Bell Report,²¹⁰ suggested that overall, those involved in the system of IRB oversight felt it was functioning efficiently and protecting participants' welfare. On the other hand, several urgent findings, as well as recommendations made by the Office of the Inspector General that same year,²¹⁹ have yet to be adequately resolved.²²⁰

For example, the Bell survey found notable differences between high-volume and low-volume IRBs in workload and time spent reviewing protocols.²¹⁰ It would be useful to examine what influence such differences have on the review process at different institutions. It also appeared that IRBs focused heavily on consent forms, with 60% of chairs reporting that the most frequent concern about consent forms had to do with overly technical language. Despite this finding and recent work confirming ongoing problems with consent form language,²²¹ meaningful modifications to promote better comprehension have

Table 6. Participant Safeguards

Theme	Relevant Papers and Findings
Ethics review committee members' views of psychiatric protocols	<ul style="list-style-type: none"> • UK study ($N = 107$ ethics review committees): informed consent, confidentiality, and certain procedures (especially placebos and washout periods) frequently raise concerns in reviews of psychiatric protocols.²³⁴
Patients' perspectives regarding specific safeguards	<ul style="list-style-type: none"> • Research participants ($N = 28$ pts with SCZ) viewed consent forms as meant to protect both themselves as participants, as well as the researcher.²³² • Pts and psychiatrists both viewed 5 safeguards (informed consent, IRB review, data safety monitoring boards, confidentiality measures, and alternative decision makers) as protective; all but alternative decision makers were viewed as positively influencing participation decisions.⁴⁶
Participant advocate procedures	<ul style="list-style-type: none"> • Survey of NIMH CATIE schizophrenia study site PIs, research coordinators, participants, and "subject advocates" (see Stroup, Bredthauer, and Appelbaum,²²⁴ in this issue). Most sites reported no specific impact of subject advocate procedures on recruitment or retention; most viewed procedures favorably. Among subject advocates, most felt the procedure helped participants to make their own decisions; among subjects themselves, half felt it positively affected their decision to enroll; a small number felt that the procedures interfered with their autonomy.
Scaling/rating of risk	<ul style="list-style-type: none"> • Pts and psychiatrists rated risks of numerous research-related procedures similarly overall, although pts rated certain procedures (eg, symptom provocation, spinal tap, and medication discontinuation for 2 weeks) as more risky, in relation to the risks encountered in the everyday lives of people with SCZ, than did psychiatrists (Roberts <i>et al.</i>, in press).⁸⁹
General public's views on mentally ill persons' ability to consent	<ul style="list-style-type: none"> • Online survey of 3140 adults (see Muroff <i>et al.</i>,¹²⁶ in this issue). Mentally ill research participants described in vignettes were viewed as less able to consent for themselves than medically ill research participants; this stigmatized perception appeared to be mediated by the belief that mentally ill people are less decisionally capable—even when the vignette described that an independent physician had deemed the patient competent.

Note: Abbreviations used: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; IRB = institutional review board; NIMH = National Institute of Mental Health; PI = principal investigator; pts = patients; SCZ = schizophrenia. Unless otherwise specified, "patients" refers to patients with schizophrenia.

yet to be adopted. In schizophrenia research specifically, we know little about the internal workings of the review and monitoring process for these protocols relative to others.

As noted above, evidence from the pediatric literature suggests substantial variability in how IRBs interpret the language of federal regulations.³⁷ In Shah *et al.*'s survey of IRB chairs, for example, investigators found that a lumbar puncture received lower mean risk ratings when the research subject was ill rather than healthy.²¹⁷ Thus, it is possible that some reviewers vary the "minimal risk" standard depending on the health status of the subject. In contrast, some commentators suggest that the definition of minimal risk should be measured against risks ordinarily encountered by healthy persons.²²²

In psychiatric research, data on differential risk assessment is available from a recent study by Roberts and colleagues. The authors examined psychiatrists' and schizophrenia patients' perceptions of the level of risk of a number of research procedures. Each procedure was described separately, not as part of an overall study, so that procedures could be compared to one another

(Roberts *et al.*, in press).⁸⁹ Participants rated the risks relative to everyday risks encountered by people with schizophrenia.

Psychiatrists and patients rated many of the procedures as having similar levels of risk, but patients rated several scenarios (eg, symptom induction, lumbar puncture, and 2-week medication discontinuation) as more risky than psychiatrists. These findings raise several points in need of further study: patients may be more attuned to risk than they are often given credit for. Conversely, researchers and review board members may rate risks differently from their subjects. Might this difference have significant effects on the protections required for psychiatric research? Without more extensive data, subjects, communities, and reviewers will not be able to conduct consistent review or construct coherent policy.^{130,223}

Another safeguard, the use of subject or participant advocates, has only recently been studied empirically (see Stroup, Bredthauer, and Appelbaum,²²⁴ in this issue). This process is designed to safeguard participants who may lack decisional capacity during enrollment in a clinical trial, or who may subsequently lose capacity.

Table 7. Ethical Issues in Schizophrenia Research: Research Agenda

Issue	Specific Topics and Questions
1. Scientific designs	<ul style="list-style-type: none"> ● Risk-benefit ratios of emerging research methods, eg, psychiatric genetics, pharmacogenomics, and presymptomatic/prodromal identification and intervention studies ● Nonbiological risks of biological, psychosocial, and services research—confidentiality, disclosure, stigmatization, legal issues; risks to “bystanders” ● Clarifying definition of vulnerability: who should be considered vulnerable and what additional safeguards should be enacted for trials enrolling these participants? ● Perspectives of participants, family members, investigators, physicians, and protocol reviewers regarding risks related to information privacy and confidentiality ● Views of, protections for, and guidelines regarding stored biological samples and brain autopsy research
2. Informed consent and decision-making capacity	<ul style="list-style-type: none"> ● Standardization and increased efficiency of capacity assessments; development of brief screening instruments ● Studying capacity longitudinally (particularly in patients with disorders whose symptoms and severity fluctuate over time, potentially causing fluctuating capacity) ● Acceptability, uses, and effects of “consent monitors” (separate from research team, who observe informed consent discussions) ● Acceptability, uses, and effects of “independent capacity assessors” (conduct capacity assessments in individuals identified as at risk of impaired decisional capacity) ● Proxy consent issues: adequacy and acceptability of proxy decision-making; issues affecting enrollment decisions by proxies; validity of proxy consent ● Psychiatric advance directives: feasibility; practical aspects; effects on enrollment, consent process, and retention; barriers to implementation ● What are the “active ingredients” in effective consent interventions? ● Studying effects of improved consent procedures on knowledge of participants, outcomes of study, recruitment, retention, and overall satisfaction with research experience ● Finding effective methods of informing participants about research procedures such as randomization and availability of alternative treatments
3. Understanding and perceptions of risk and benefit-seeking (including the therapeutic misconception)	<ul style="list-style-type: none"> ● Perceptions of potential risks (relevance, severity) by stakeholders (patients, families, psychiatrists, researchers, research staff, institutional review board members, community at large) ● Assessing and addressing therapeutic misconception (in participants and investigators)
4. Influences on research participation	<ul style="list-style-type: none"> ● Study recruitment procedures: ethical issues/norms (for both publicly and privately funded studies) ● Improving recruitment of groups underrepresented in research ● Advertising for clinical studies: stakeholders’ perceptions of advertising, effects of advertising, guidelines regarding advertising, eg, are guidelines followed? ● What information do potential participants want to know? What would a “reasonable person” want to know? What risks do they consider most relevant? Which information do they disregard? What matters to whom, and why? ● Influences on participation decisions (eg, understanding of the protocol, risk-benefit ratio and the individual’s perception thereof, risk tolerance, attitudes toward and experiences with research, type and level of compensation offered, input from family or significant others) ● Research on voluntarism: developing and assessing measures to assess this aspect of informed consent ● Psychiatric advance directives for research: efficiency, feasibility, effects ● Reasons for study refusal ● Cultural issues (including language barriers) in recruitment, including issues of trust in research as a whole, understanding of research goals and methods, and involvement of families/community in participation decisions
5. Participant safeguards	<ul style="list-style-type: none"> ● Studies of institutional review board processes and training ● Clarifying the basis for and consistency of institutional review boards’ scaling of risk ● Are levels of review and safeguards commensurate with the level of risk?

In its recommendations the National Bioethics Advisory Commission (NBAC) relied on the use of an ill-defined “legally authorized representative (LAR)” for consent to certain procedures (ie, minimal risk or greater than minimal risk with the prospect of direct benefit). But NBAC would only allow an LAR to enroll an incapable subject if the subject had previously provided authorization. This would require an uncommon degree of prescience on the part of patients and investigators. Leaving aside for the moment the difficulties of determining “minimal” risk and the “prospect” of direct medical benefit, the use of the subject advocate contains many layers of subtlety that have been insufficiently studied, from the standards of capacity assessment to the timing and procedures of surrogate involvement. The work of Stroup and colleagues is therefore highly informative, as it is the first empirical study of subject advocate procedures actually enacted for schizophrenia research.

Conclusion

Although it is not possible to touch on every conceivable area of research ethics in schizophrenia, we have attempted to survey the landscape of recent and emerging findings. Built on the foundation of early studies conducted by pioneers in empirical ethics (whose work is well represented in this issue of *Schizophrenia Bulletin*),^{42,44,84,163} recent conceptual and empirical work has begun to tackle important questions. These endeavors include exploring the dimensional and categorical aspects of decision-making capacity, detailing the correlates of decision-making capacity, making inroads into enhancing informed consent procedures, bringing forth the previously unheard voices and perspectives of patient-participants themselves, and highlighting the varied needs of participants, families, and their communities.

As schizophrenia research expands and advances in new directions—many of which will bring novel and unexpected ethical challenges—the diverse and vital field of empirical ethics can only improve the collaboration between patients, communities, and researchers. As Table 7 highlights, much remains to be done. We hope that this review informs and stimulates the discussion and future work needed to advance the field.

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