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Longitudinal consent-related abilities among research participants with schizophrenia: Results from the CATIE study

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Abstract

Objective—Research participants must have adequate consent-related abilities to provide informed consent at the time of study enrollment. We sought to determine if research participants with schizophrenia maintain adequate consent-related abilities during a longitudinal study. If participants lose abilities during a trial they may not be able to judge and protect their interests. If reduced abilities are common or can be predicted, special protections can be targeted appropriately.

Method—We examined longitudinal consent-related abilities of participants in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study using the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) at protocol-specified times over 18 months.

Results—Of 1,158 research participants in this analysis, most (n= 650, 56%) had a stable pattern of MacCAT-CR Understanding scores, 235 (20%) improved substantially with no evidence of decline, 273 (24%) had at least one assessment with substantial worsening. During the course of the trial, 43 (4%) fell below the initial threshold for adequate capacity, which was predicted by lower Understanding scores, more severe positive symptoms, and poorer neurocognitive functioning at baseline, and by increases in negative symptoms and deteriorating global status.

Conclusions—Most participants in this long-term study had stable or improved consent-related abilities, but almost one-fourth experienced substantial worsening and 4% of participants fell below the study's capacity threshold for enrollment. Clinical investigators should monitor with special care individuals with marginal capacity or higher levels of psychotic symptoms at study entry and those who exhibit clinical worsening during a study.

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Introduction

The severity and fluctuating course of schizophrenia have led to questions about the abilities of affected individuals to provide informed consent to participate in research studies and concerns about the validity of such consents (National Bioethics Advisory Commission 1998; Appelbaum 2006). Researchers have shown that most people with schizophrenia have adequate consent-related abilities to consent to research (Carpenter, Gold et al. 2000), but little is known about the durability of such abilities in long-term studies or about the correlates of changes in these abilities.

Previous research has shown that the consent-related abilities of individuals with schizophrenia are worse than non-ill comparison subjects, subjects with depression, and those with HIV (Carpenter, Gold et al. 2000; Moser, Schultz et al. 2002). Of particular interest is the observation that the capacity for research participation among individuals with schizophrenia is not static. In one study most individuals who initially demonstrated impaired decision-making capacity were later judged capable of making an adequate decision after participating in a focused educational intervention (Carpenter, Gold et al. 2000). On the other hand, a study of 10 research participants with schizophrenia found only small changes in measures of capacity over two weeks while antipsychotic medications were systematically stopped as part of a study protocol (Moser, Reese et al. 2005), although longer periods of monitoring might have detected larger changes.

A number of researchers have examined the correlates of consent-related abilities and decision-making capacity (Stroup, Appelbaum et al. 2005; Dunn, Candilis et al. 2006). Overall neurocognitive functioning has been the most consistent correlate, while positive and negative symptoms of schizophrenia have shown inconsistent associations. Negative symptoms have been a more consistent correlate of poor capacity than have positive symptoms, but high levels of positive symptoms, including disorganization, may affect the capacity to consent to participate in research (Dunn, Nowrangi et al. 2006).

If consent-related abilities fluctuate along with the course of illness, participants in long-term studies may not be able to judge or protect their own interests. For example, they may not be able to recognize or report the occurrence of side effects to the investigators, or to decide when it might be appropriate for them to withdraw from the study. If a significant proportion of research participants with schizophrenia lose substantial consent-related abilities, it would be useful to be able to identify those at risk so that safeguards could be put in place to protect their interests, while allowing researchers, where appropriate, to proceed with the study in question and answer important scientific questions. Among possible safeguards would be targeted screenings for loss of capacity and, in the event the participant is no longer capable, the appointment of advocates to monitor participants' conditions, facilitate communication with investigators, and make decisions on participants' withdrawal from the studies.

We conducted this investigation to examine changes in consent-related abilities over time, to determine the frequency of diminished abilities, and to identify predictors of change, so that the need for additional protections of this sort might be better assessed. Based on previous studies (Stroup, Appelbaum et al. 2005; Dunn, Candilis et al. 2006), we predicted that changes in neurocognitive functioning and negative symptoms would be strong correlates of variations in consent-related abilities, but that positive psychotic symptoms would correlate less strongly.

Methods

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, funded by the National Institute of Mental Health, enrolled 1493 persons with schizophrenia at 57 U.S. sites (Stroup, McEvoy et al. 2003). Prospective subjects who consented for screening then had to demonstrate adequate decision-making capacity to receive randomly assigned antipsychotic medication. The judgment of decision-making capacity by the researcher was aided by the MacArthur Competence Assessment Tool—Clinical Research (MacCAT-CR)(Appelbaum and Grisso 2001). Both inpatients and outpatients were eligible; individuals were considered appropriate for the study if their current antipsychotic treatment was suboptimal due to either efficacy or tolerability concerns. The study took place at sites in the U.S. intended to represent typical settings in which people with schizophrenia receive treatment. The 57 U.S. clinical sites included 16 university clinics, 10 state mental health agencies, 7 Veterans' Affairs (VA) Medical Centers, 6 private non-profit centers, 4 private practice sites, and 14 mixed system sites. Investigational Review Boards at each site approved all study procedures; written informed consent was obtained from subjects or their legal guardians.

Measures

CATIE schizophrenia trial participants received the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) at the time of enrollment in the CATIE trial, after 6 and 18 months of study participation, and at any time a study antipsychotic medication was discontinued. The MacCAT-CR evaluates the following four abilities related to capacity to consent to research: 1) Understanding--the ability to understand relevant information; 2) Appreciation--the ability to appreciate the situation and its likely consequences; 3) Reasoning--the ability to reason (i.e., to manipulate information rationally); and 4) Choice--the ability to communicate a choice about participation (Appelbaum and Grisso 2001). Each ability is assessed by specific questions with answers rated on a 0-2 scale with 0 reflecting no comprehension, 1 partial comprehension, and 2 indicating full comprehension of the relevant concept. The Understanding scale has 13 questions (range 0-26), the Appreciation Scale has three questions (range 0-6), the Reasoning scale has four questions (range 0-8) and the Choice scale has only one question (range 0-2). The instrument has been widely used in research and is described in detail elsewhere (Carpenter, Gold et al. 2000; Appelbaum and Grisso 2001; Palmer, Nayak et al. 2002; Moser, Reese et al. 2005; Moser, Reese et al. 2006). At present, the MacCAT-CR is the most widely used and best validated of the competence assessment instruments, including with subjects with schizophrenia (Palmer and Savla 2007).

The MacCAT-CR was administered by research personnel who participated in training sessions at investigators' meetings that were held before the study began and again 15 months after enrollment began. Refresher training materials were available online throughout the study. In previous studies involving individuals with schizophrenia, the instrument was reliably scored by similarly trained individuals (Carpenter, Gold et al. 2000; Kovnick, Appelbaum et al. 2003). An Understanding score of 16 or higher on the 26-point scale was required as a minimum for study randomization, although clinical judgment was the final determinant of competence to consent even if a subject achieved this threshold. This threshold reflected an *a priori* judgment by the CATIE investigators of what constituted minimally adequate understanding of this specific research protocol. Although the minimum required score was selected *a priori*, independent analyses of MacCAT-CR interviews conducted among individuals with a broad range of illness severity to determine the appropriate trade-offs of sensitivity and specificity suggested that this was an appropriate threshold for the subjects who enrolled in the CATIE study (Kim, Appelbaum et al. 2007). The Understanding scale was used to establish the threshold of capacity because

Understanding generally correlates highly with Appreciation and moderately with Reasoning, and—given its greater range—has the strongest psychometric properties of the three scales (Kovnick, Appelbaum et al. 2003; Kim, Appelbaum et al. 2007).

Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), which includes positive, negative, and general psychopathology subscales (Kay, Fiszbein et al. 1987). Neurocognitive functioning was measured by separate test scores, that were converted to z-scores and combined to construct five separate scales that were themselves averaged to form a Neurocognitive Composite Score, as described in a previous publication (Keefe, Mohs et al. 2003). The five scales were 1) *Processing Speed*, the average of Grooved Pegboard, the WAIS-R digit Symbol Test, and the average of the Controlled Oral Word Association Test (COWAT) and Category Instances; 2) *Verbal Memory*, the average of three trials of the Hopkins Verbal Learning Test; 3) *Vigilance*, based on the Continuous Performance Test (CPT) d-prime scores (average of 2-digit, 3-digit, and 4-digit); 4) *Reasoning*, the Average of Wisconsin Card Sorting Test and WISC-R Mazes; and, 5) *Working Memory*, the average of a computerized test of visuospatial working memory (sign reversed) and letter number sequencing. Subjective attitudes toward treatment were measured using the Drug Attitude Inventory (Hogan, Awad et al. 1983; Awad 1993). Symptoms of depression were measured using the Calgary Depression Scale for Schizophrenia (Addington, Addington et al. 1990).

Data Analysis

The analyses included all study participants who had baseline and at least one post-baseline score on the MacCAT-CR. To compare the participants in the analysis with the ones excluded because of the absence of post-baseline measures, we examined demographics and baseline symptom measures, using two-sided Fisher's exact tests for categorical variables and two-sided Kruskal-Wallis tests for continuous variables.

We defined 'substantial change' as a one standard deviation increase or decrease from baseline, applied to the three MacCAT-CR categories, and rounded to whole numbers. The criteria for significant change were thus three points for the Understanding score and two points for the Reasoning and Appreciation scores. Participants were categorized into one of three groups; 1) Stable: participant had no significant change from baseline; 2) Improved only: participant had significant improvement and no significant decline; 3) Declined: participant experienced a significant decline at some point in the trial (regardless of whether an increase also occurred). Based on all available data for each participant, each person was categorized into only one of the three groups. The small number of subjects whose scores fluctuated substantially in both directions (n=25) were included in the Declined group, since the possible loss of decisionmaking capacity was the outcome of greatest interest in this study.

Repeated measures mixed models explored the demographic, clinical, and treatment variables associated with MacCAT-CR score changes at 6 and 18 months. Based on prior knowledge of the potential associations among specific covariates, we organized the covariates in three tiers: 1) demographic variables of age, gender, race and ethnicity, and exacerbation status and tardive dyskinesia status at baseline; 2) type of clinical setting (VA, private, university, non-profit, state mental health hospital, mixed) and baseline cognitive and clinical variables, including years of education, substance use, anticholinergic medication use, as well as baseline scores of MacCAT-CR, the Calgary Depression Scale, the cognitive functioning summary score, and PANSS positive and negative symptom scores; 3) time-dependent longitudinal measures at follow up visits, including antipsychotic medication, substance use, changes in PANSS positive and negative scores from baseline, Calgary Depression Scale score change, and anticholinergic medication use. The model

building process started with a backward selection within each tier at an initial threshold level of $p < 0.05$ to ascertain variables with unique predictive associations with MacCAT-CR score change. We then performed the second-level model selection by an omnibus regression in which variables found to contribute significantly within each tier were considered together. The second-level backward model selection identified unique predictors in the final model with a significance level of 0.01 to control for Type I error.

The analysis to predict patients at risk of falling below the critical decision-making capacity threshold was done using a logistic regression with a MacCAT-CR Understanding score below 16 as the target event. The exploratory model building procedure followed a similar strategy as outlined for the mixed model with three tiers of covariates and a two-level backward variable selection procedure, first within each tier and then for the omnibus regression model.

The analyses were conducted using SAS 9.1, Cary, NC.

Results

Demographics

The analysis included longitudinal MacCAT-CR data on 1158 participants with a baseline and at least one post-baseline MacCAT-CR measure. The mean $\pm$ SD duration of study participation for the included subjects was 12.5 $\pm$ 6.1 months. Those included were more likely to be Caucasian, had slightly higher baseline scores on the MacCAT-CR Reasoning scale, and slightly higher educational achievement (Table 1) than participants who were not included in the analysis because they provided no follow-up data. There were no differences in levels of symptoms or any other clinical or demographic variables.

Correlates of MacCAT-CR Score Changes

Examinations of predictors of MacCAT-CR subscale score changes produced mostly consistent results for Understanding, Reasoning, and Appreciation scores, but with certain variations for the different subscales (Table 2). The correlates of the MacCAT-CR Understanding subscale score changes were neurocognitive functioning at baseline, changes in neurocognitive functioning, positive and negative symptoms, the baseline Understanding score, and type of clinical setting. Better neurocognitive functioning at baseline was associated with more Understanding score improvement during the trial while deteriorating positive and negative symptoms were predictors of deteriorating Understanding scores. Participants with high Understanding scores at baseline demonstrated less improvement during the trial, possibly due to a ceiling effect that left little room for further improvement. Participants in university clinics experienced less improvement and participants in private clinics experienced more improvement in the MacCAT-CR Understanding score compared to participants in other settings.

The analyses of correlates of the MacCAT-CR Reasoning subscale score revealed substantial overlap with the Understanding subscale analyses: baseline Reasoning score, neurocognitive functioning at baseline, changes in positive symptoms, and drug attitude all followed the same trends as they had in the analyses of the Understanding subscale. Better neurocognitive functioning at baseline predicted more improvement in the Reasoning score. Deteriorating symptoms were associated with deterioration in Reasoning scores, while increasing scores on the Drug Attitude Inventory, indicating a more favorable attitude toward antipsychotic medications, was associated with improving Reasoning scores. Again, higher baseline Reasoning scores were associated with less improvement due to a ceiling effect. Participants in VA and university hospitals experienced less improvement in the Reasoning score than participants in other settings.

Finally, as with the both the Understanding and Reasoning subscales, better neurocognitive functioning at baseline was associated with more Appreciation score improvement, while positive symptom deterioration was associated with declining Appreciation scores. The ceiling effect of high baseline scores was replicated again for the Appreciation scores.

Prediction of Lost Decision-making Capacity

During the trial, 43 (4%) participants fell below the *a priori* decision-making capacity threshold (MacCAT-CR Understanding subscale score of 16 or above) required for randomization to a study medication. The predictors of falling below the threshold were consistent with the continuous mixed models predicting MacCAT-CR subscale score changes. The model parameters with estimated odds ratios are listed in Table 3. Lower baseline Understanding scores predicted higher likelihood of falling below the threshold, meaning that proximity to inadequate capacity at baseline predicted loss of capacity later. Poorer baseline neurocognitive functioning and higher levels of positive symptoms at baseline also predicted falling below the threshold. Worsening overall psychopathology, and worsening negative symptoms in particular, during the course of the trial also predicted falling below our threshold score for adequate decision-making capacity.

Effect of Study Antipsychotics

In our models, there were no differences in changes in consent-related abilities or in loss of capacity based on which antipsychotic drug subjects received; all subjects, however, were treated with antipsychotic medication, since that was the main focus of the CATIE study.

Discussion

This is the first large-scale investigation of the longitudinal consent-related abilities of research participants diagnosed with schizophrenia. We found that most participants (96%) in the CATIE schizophrenia trial, who had demonstrated adequate decision-making capacity at the time of consent, maintained this capacity, and many (20%) demonstrated improvements in consent-related abilities over time. However, 23% had substantial adverse changes in their scores, indicating possible decrements in their ability to act in their own interests, although the significance of these declines is not clear. In addition, 4% of participants who met our *a priori* threshold for adequate capacity at study entry later no longer met this criterion.

Earlier analyses from this study (Stroup, Appelbaum et al. 2005) had echoed the findings in prior research showing that neurocognitive function and negative symptoms were significantly related to baseline performance on measures of decisional abilities, whereas such a relationship was usually absent for positive symptoms (Carpenter, Gold et al. 2000; Dunn, Lindamer et al. 2002; Moser, Schultz et al. 2002; Kovnick, Appelbaum et al. 2003; Palmer, Dunn et al. 2004; Palmer, Dunn et al. 2005). The analyses presented here extend those findings to demonstrate that adverse changes in neurocognitive tests and negative symptoms during the study are associated with decreased consent-related abilities. Because neurocognitive deficits appear mostly stable in individuals with schizophrenia (Heaton, Gladsjo et al. 2001), it is notable that adverse changes in neurocognition are reflected in consent-related abilities. In addition, increases in positive symptoms during the study also correlated with decrements in these abilities, suggesting that positive symptoms are important in assessing the likelihood that subjects will manifest impairment in decisional tasks.

The finding that white participants were less likely to fall below the decisionmaking capacity threshold than those of other races is a new finding that was unexpected. Because

previous research using the MacCAT-CR has not reported racial differences, effects of race and ethnicity should be explored in other investigations. Clinical researchers must take care to ensure that the interests of participants of all races and ethnicities are protected.

As a practical matter, the results from this study do not suggest that all persons with schizophrenia participating in a longitudinal trial require special procedures, such as formal re-testing of consent-related abilities, as a trial progresses. It is reassuring that roughly three quarters of participants retained their initial level of capacity or showed improvement. However, roughly one quarter of participants lost some of their consent-related abilities and arguably some of their capacity to protect their own interests in the context of a protocol-driven longitudinal research study. Given that important research questions apply to such individuals and that it is important to include them in studies if possible, consideration should be given to providing safety measures to ensure their interests are protected.

When a study participant worsens in some clinically important way, investigators must judge whether that participant is still suitable to continue in the study as before or whether additional protections of the participant's interests are needed. These decisions will turn in part on the extent to which the participant's decisional abilities have diminished. Periodic reassessment of all persons with schizophrenia who were judged capable of initial consent to research does not appear to be indicated by our data. Rather, such inquiry can be focused on subjects who demonstrate poor understanding at baseline, with increases in psychotic symptoms and, if data are available, decrements in neurocognitive performance.

Researchers and Institutional Review Boards are still gaining experience with the kind of protections that might be put into place when decisional capacity is lost. Greater involvement of a third party devoted to the participant's interests might be warranted. As an example of how this might work to protect patients' interests, in the CATIE trial we asked each subject to designate a "subject advocate" (Stroup and Appelbaum 2003). Subject advocates were family members, friends, or someone else not involved in the research who participated in the initial consent discussion and assisted with decision making. Subjects made the initial decision about enrollment, but subsequently, if a subject's decision-making capacity lapsed, consultation with the subject advocate was required. The subject advocate could then withdraw the participant from the study if the criterion of an adverse change in the risk/benefit ratio had been met. However, the subject advocate could permit a subject whose decision-making capacity had lapsed to remain in the study if the individual wanted to continue and the risk/benefit ratio had not been significantly and unfavorably altered. These procedures were viewed favorably by research personnel, subject advocates, and by research participants themselves, and overall were judged not to have a negative impact on study recruitment, subject autonomy, or subject retention (Stroup and Appelbaum 2006).

Limitations

The CATIE study, the largest of its kind, used a well-validated instrument to assess consent-related abilities. All raters were trained and re-trained in the use of the MacCAT-CR but were not required to achieve a standard level of reliability. Previous studies using similar training procedures had found ratings to be reliable (Carpenter, Gold et al. 2000; Kovnick, Appelbaum et al. 2003). While results regarding the relationship between consent-related abilities and neurocognition and symptoms were quite consistent in all of our analyses, there were inconsistently significant relationships between type of site and MacCAT-CR subscale performance. In spite of our training procedures, these site variations may be related to inter-rater variability. It is also possible that these results reflect differences in patients or practice patterns between settings beyond the demographic and clinical characteristics that we were able to control for in our models.

Although the MacCAT-CR is well-validated, it has limitations. Only the Understanding score with 13 items has a substantial range of possible scores while the small number of items on the Appreciation and Reasoning scales lead to considerable instability of psychometric properties. This may help account for the larger percentage of individuals who changed one standard deviation on the Reasoning scale.

Another limitation is that 302 of 1460 study participants left the study early and did not provide any longitudinal data. It is possible that the early dropouts represent a group experiencing clinical circumstances, such as worsening symptoms, associated with more adverse changes in decision-making capacity. Hence, these data may underestimate the likelihood of research participants with schizophrenia suffering decrements in consent-related abilities or losing capacity during the course of a clinical trial. Moreover, the criterion for decisional capacity was selected *a priori* by the leaders of the research team, though subsequent analyses with independent psychiatrists rating the competence of a sample of the participants suggested that the threshold was an appropriate choice for this population (Kim, Appelbaum et al. 2007). In addition, because there was a known threshold score required for study entry, study personnel may have had an incentive to score an individual's responses high to enable enrollment. However, if this had any impact at baseline it should not have had an effect subsequently because there was no required threshold score for continued participation due to the subject advocate mechanism that was in operation.

Conclusions

Most individuals who demonstrated adequate capacity to provide informed consent in this study, which included only active treatment arms, maintained adequate capacity throughout their period of participation. However, clinical investigators should be aware that individuals with marginal capacity at study entry and increased levels of symptoms or other evidence of global clinical deterioration during the study are at increased risk of lost capacity. Investigators should monitor the ability of such participants to provide meaningful informed consent on an ongoing basis. In studies that aim to enroll severely ill patients or those with substantial cognitive impairment who are at most risk of lost capacity, specific procedures to protect the interests of these subjects may be warranted.

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Table 1

Baseline Demographic and Clinical Characteristics

Variable	Total (N= 1460)	Excluded (N= 302)	Analysis (N= 1158)	P-Value
Age [Mean(SD)]	40.55 (11.10)	39.69 (11.07)	40.78 (11.11)	0.1364
Gender				
Female [N(%)]	380 (26.03%)	71 (23.51%)	309 (26.68%)	0.2705
Male [N(%)]	1080 (73.97%)	231 (76.49%)	849 (73.32%)	.
Race				
White Only [N(%)]	874 (59.86%)	151 (50.00%)	723 (62.44%)	0.0004
Black Only [N(%)]	513 (35.14%)	134 (44.37%)	379 (32.73%)	.
Other [N(%)]	73 (5.00%)	17 (5.63%)	56 (4.84%)	.
MacCAT				
Understanding [Mean(SD)]	23.61 (2.69)	23.80 (2.60)	23.56 (2.71)	0.2074
Reasoning [Mean(SD)]	5.79 (1.92)	5.44 (1.97)	5.88 (1.90)	0.0003
Appreciation [Mean(SD)]	4.77 (1.27)	4.67 (1.39)	4.79 (1.23)	0.4109
PANSS				
Total [Mean(SD)]	75.66 (17.56)	77.18 (17.19)	75.27 (17.63)	0.133
Positive [Mean(SD)]	18.47 (5.63)	19.12 (5.64)	18.30 (5.62)	0.0547
Negative [Mean(SD)]	20.17 (6.41)	20.36 (6.39)	20.13 (6.42)	0.5823
General [Mean(SD)]	37.02 (9.31)	37.71 (9.14)	36.84 (9.34)	0.2195
CGI [Mean(SD)]	3.96 (0.94)	3.93 (0.90)	3.96 (0.95)	0.3962
Years since first treatment [Mean(SD)]	16.51 (10.96)	16.38 (10.3)	16.55 (11.13)	0.9602
Years since first prescription [Mean(SD)]	14.41 (10.70)	14.50 (9.95)	14.39 (10.88)	0.5378

Table 2
Significant Clinical Correlates of MacCAT-CR Score Change: Final Mixed model with Repeated Measures

Effects	Understanding		Reasoning		Appreciation		Total	
	Estimate(SE)	p	Estimate(SE)	p	Estimate(SE)	p	Estimate(SE)	p
Baseline MacCAT Score	-0.65(0.029)	<.001	-0.53(0.027)	<.001	-0.64(0.029)	<.001	-0.55(0.028)	<.001
VA Hospital			-0.74(0.15)	<.001				
University Hospital	-0.52(0.19)	0.008	-0.62(0.13)	<.001			-1.16(0.30)	<.001
Private Clinic	0.91(0.32)	0.004						
Baseline Neurocognitive Summary Score	0.54(0.083)	<.001	0.20(0.052)	<.001	0.28(0.036)	<.001	0.99(0.13)	<.001
Change in Neurocognitive Summary Score	0.50(0.14)	<.001					0.91(0.22)	<.001
Change in PANSS Positive Score	-0.041(0.013)	0.002	-0.037(0.0087)	<.001	-0.027(0.0059)	<.001	-0.095(0.02)	<.001
Change in PANSS Negative Score	-0.056(0.013)	<.001					-0.08(0.02)	<.001
Change in Drug Attitude Inventory Total Score			0.036(0.013)	<.001				
Visit Difference: 6 months vs. 18 months	0.37(0.10)	<.001					0.49(0.16)	0.003

Each model followed a backward selection process from 3 tiers of potential correlates including demographic, clinical, and treatment variables. The estimates (SE) are model-predicted MacCAT-CR score changes associated with each categorical effect or 1 unit change of each continuous measurement.**

Table 3

Significant Clinical Correlates of Falling below Decisionmaking Capacity Threshold during Study: Final Logistic Regression Model

Effect	Odds Ratio Estimate	95% Wald Confidence Limits	P
Race (White)	0.361	0.174	0.0063
Baseline MacCAT-CR Understanding	0.761	0.682	<.0001
Baseline Neurocognition Summary Score	0.542	0.375	0.0012
Baseline PANSS Positive Symptom Score	1.104	1.038	0.0018
PANSS Negative Symptom Deterioration	1.143	1.076	<.0001
CGI Score Deterioration	1.493	1.066	0.0197

The model followed a backward selection process from 3 tiers of potential correlates including demographic, clinical, and treatment variables. The odds ratio estimates are model-predicted odds ratios associated with each categorical effect or 1 unit change of each continuous measurement. •