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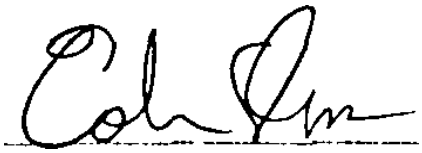
May 17, 2019

Re: Cover Letter for Clinical Trials.gov NCT 02035202 (Depp)

This Cover Letter accompanies Study Protocol for this trial NCT012035202 which completed.

Sincerely,



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STUDY PROTOCOL

1. PROJECT TITLE

A Clinical Trial of Mobile Telephone based Assessment and Intervention for Persons with Bipolar Disorder or Schizophrenia

2. PRINCIPAL INVESTIGATOR

PI: Colin A Depp, Ph.D., Associate Professor, Department of Psychiatry

3. FACILITIES

UCSD Medical center; UCSD La Jolla campus

4. ESTIMATED DURATION OF THE STUDY

5 Years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The purpose of this study is to evaluate the effectiveness of a mobile real-time cognitive behavioral intervention for serious mental illness (SMI) and to identify the facilitators, barriers, and costs of implementation. We would like to determine whether the addition of a mobile phone monitoring software program to a brief behavioral intervention for bipolar disorder or schizophrenia improves symptoms arising from the disorders. In this study we will be assessing the feasibility, acceptability and short term effect of the mobile phone enhanced intervention for bipolar disorder and schizophrenia. In addition, we will gather data from self-report measures and neuroscience-based tests from participants to inform future efforts in designing interventions aimed at diminishing risk of suicide in this population.

6. SPECIFIC AIMS

The goal of the study is to evaluate the effectiveness of a mobile real-time cognitive behavioral intervention for serious mental illness (SMI) and to identify the facilitators, barriers, and costs of implementation.

Our intervention called CBT2go builds on our extensive preliminary work using mobile devices, integrating ecological momentary assessment (EMA) with CBT content in BD and SZ. EMA is an ambulatory data collection technique[1-3] that allows the *in vivo* assessment of moods, symptoms, medication adherence, social interactions and other daily activities. CBT2go delivers personalized thought challenging and behavioral coping interventions based on EMA's real-time reports. CBT2go is a 12-week intervention that involves a single in-person session followed by personalized yet automated responding on a mobile device, targeting affective and psychotic symptoms, medication adherence, socialization, and relapse prevention.

We are proposing a 6-month randomized controlled trial, with 255 participants recruited from the San Diego County public mental health system who have no current access to CBT. Participants will be stratified by diagnosis (BD or SZ), and will be randomized to receive CBT2go, EMA only, or Standard Care. This design will evaluate the added benefit of CBT components over EMA only (device contact, medication reminders, symptom monitoring), as well as the benefits of these components relative to Standard Care. Individuals will be assessed at baseline, mid-point (6 weeks), post-treatment (12 weeks) and 3-month follow up (24 weeks). Our primary and secondary outcomes will be measured with lab-based clinical ratings as well as EMA-based outcomes. We will also identify moderators (diagnostic group, cognitive ability) and mechanisms of change with respect to the elements of CBT

theory (changes in insight and dysfunctional attitudes). To inform pathways to implementation, we will evaluate the costs, barriers and facilitators to adopting CBT2go, with innovative methods from our implementation research. In addition, we would like to perform multiple blood draws on a subset of BD participants to determine whether variability in inflammatory markers, mood and cognitive performance predicts future suicide ideation in this population.

Aim 1 (Effectiveness): To determine the impact of CBT2go on primary and secondary outcomes.

Hypotheses 1 (Primary Outcome): Compared to EMA and Standard Care, the CBT2go intervention will be associated with greater improvement in global psychopathology (as measured by BPRS Total Score).

Hypotheses 2 (Secondary Outcomes): Compared to EMA and Standard Care, the CBT2go intervention will be associated with greater improvement in EMA and standard lab-based measures of medication adherence, social functioning, and hospitalization and emergency service utilization.

Aim 2 (Moderators and Mediators): To determine the impact of moderators and mechanisms on outcomes.

Hypothesis 3 (Cognitive Impairment and Diagnosis): Neurocognitive ability will account for more variation in device compliance and treatment response than diagnostic group.

Hypothesis 4 (Awareness and Attitudes): Improvement in illness awareness and reduction in dysfunctional beliefs will mediate incremental benefit of CBT2go over comparison conditions.

Exploratory Aim 3: Explore a predictive model for suicidal ideation in bipolar disorder that includes direct and indirect effects of cognitive performance, inflammatory cytokine levels, and trajectories of negative affect.

Supplement Aim 1: To evaluate the association between baseline trait and dynamic impulsivity/social threat with lifetime suicide risk and intensity of and intra-individual variability in suicidal ideation

Hypothesis 1: Impaired performance on impulsivity and social threat measures will be associated with higher lifetime rates of suicide attempts, and more severe and more variable suicidal ideation over 24 weeks
Exploratory: We will examine these effects by diagnostic group and treatment group assignment

Supplement Aim 2: Test the accuracy of prediction models with intensive longitudinal data in the two-week window of time before increases in suicidal ideation

Hypothesis 2: Accuracy of our prediction method will be greater than AUC=0.85 in predicting increases and will be greater than that associated with baseline suicide risk

7. BACKGROUND AND SIGNIFICANCE

Schizophrenia (SZ) and bipolar disorder (BD) are among the top ten causes of disability in the United States[4], produce approximate excess mortality of 20 years per person[5,6], and together cost over 100 billion dollars per year[7,8]. Meta-analyses of cognitive behavioral therapy (CBT)[9-12] for BD and SZ indicate clinically significant improvements in symptoms and reductions in disability. Nevertheless, at present, less than 5% of patients with SMI receive any evidence-based psychotherapies including CBT[13]. Policy changes may continue to shrink access (e.g., California's Medicaid stopped reimbursing for most psychological services in 2009). Implementation of CBT for SMI faces major barriers including the small geographically restricted pool of trained providers and its resource intensity (e.g., 20 in-person contacts). Our preliminary studies indicate mobile technology can deliver

low intensity personalized cognitive behavioral intervention that is feasible, acceptable, and effective in BD and SZ[14,15]. If mobile interventions can produce the same effects as in-person CBT, more people with SMI could gain access and benefit at 15-20% of the cost.

Individuals with BD and SZ are also at a greater risk for suicidal behavior[16] and often display altered levels of inflammatory cytokines[17] and deficits in cognitive processing[18-20]. Several studies have linked inflammation to suicidal behavior[21-23] and cognitive decline[24-26]. Further, altered cognitive processing has also been demonstrated in suicidal individuals[18-20]. However, less is known about relationship between cytokine levels, cognitive performance, and suicidal ideation in BD. The potential mediating role of fluctuations in mood state (as measured by the EMA technology), inflammatory status and cognition will also be addressed in order to understand neurobiological aspects of suicidality in BD and develop sensitive, but straightforward, markers of suicide risk.

Relatedly, emerging theories of near-term suicide risk posit that aberrant decision making in the realm of risk taking may be associated with elevated likelihood of suicidal ideation and behavior. People with BD and SZ are at risk for impulsive decision making, which may be a trait like aspect of these illnesses as well a state-like variable that fluctuates along with psychiatric symptoms. Moreover, dysfunctional social beliefs, such as the overperception of threat in other people, may also contribute to social isolation and risk of suicidal thoughts. Thus, dysfunctional social beliefs and impulsivity may help explain the elevated risk of suicidal thinking in bipolar disorder and schizophrenia, and can be assessed with objective laboratory based tests performed via computer as well as by self report. No studies to our knowledge have linked these two constructs to suicidal thoughts in serious mental illnesses and our clinical trial provides a unique opportunity to gather data on these constructs in the context of the other data gathered already. The National Institute of Mental Health and the National Strategy for Suicide Prevention detail a high priority in leveraging ongoing data resources to aid in understanding near term suicide risk in populations with high base rates of suicide (such as people with serious mental illnesses).

8. PROGRESS REPORT

We are in Year 3 of the 4 year NIMH Award and have recruited and randomized 143 people out of the targeted 255 participants. We have submitted all required data to our sponsor, the NIMH, and have met or exceeded all recruitment targets to date. There are approximately 112 more people to randomize. We have had excellent retention in the trial (96%) and we have had no complaints from participants. We have not reported any data from this trial as the randomization is not locked. The study is listed on Clinical Trials.gov and its actively recruiting.

There have been no Adverse Events in our research study. We have participated in two annual DSMB meetings, the most recent of which was in January 2015. The board voted to approve the study and raised no concerns that required changing any of the protocols, commending the study on its success in recruiting and retention of participants.

9. RESEARCH DESIGN AND METHODS

Participants: The subject population in this study will be a total of 255 men and women, with DSM-IV TR diagnoses of bipolar disorder I (BD), schizophrenia (SZ), or schizoaffective disorder, who reside in San Diego. Our inclusion and exclusion criteria were selected in order to increase the generalizability of our sample and broad reach of the mobile intervention. Participants will be of either gender and any race/ethnicity, with an age range of 18-65 years

We may enroll participants who are currently participating in other studies, where the PI of this study (Colin Depp, Ph.D.) is a co-investigator. Specifically, some of our participants maybe concurrently enrolled in "*Psychosis and Aging*" (HRPP# 101631, P.I. Jeste) or *"Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder"* (HRPP #141474, P.I. Eyler). There is overlap between the assessments of those studies and this protocol. Thus, in order to reduce participant burden, we will use existing data from those studies instead of asking participants to repeat a recently completed assessment battery. Participants will be informed of this as part of the informed consent process.

Participant Inclusion/Exclusion Criteria: Participants will be required to have a minimum level of impairment on at least one of the target outcomes, defined as a score of ≥ 3 (moderate) on the BPRS depression, mania, hallucinatory behavior, or sociality items. Prior to study entry, participants will be on stable medications, defined as the same regimen for at least 60 days and a constant therapeutic dose for at least 30 days. Patients enrolled in any current psychotherapy or with prior exposure to CBT within the past 5 years will be excluded. All participants must be willing to sign a release of information form in order for study staff to be able to inform treating clinicians of symptom exacerbations/suicidality. We will exclude participants who are not English-speaking, and in the future we will program CBT2go in other languages (e.g., Spanish). Participants must also be able to read and manipulate the touch screen device, assessed via direct observation and Snelling eye chart performance. Participants with a diagnosis of dementia or head trauma with loss of consciousness for greater than 30 minutes will be excluded. The study population is at risk for diminished capacity to consent to research, so participants will be assessed for capacity to consent for this study with the UBACC test[27], developed at UCSD.

Randomization: Participants will be randomized to CBT2go, EMA-only or Standard Care, stratified by diagnosis (BD v. SZ).

Participants will receive $70 dollars at each assessment (weeks 0, 6, 12, & 24) and a bonus $50 if they complete at least 3 assessments for a total of $330 if all assessments are completed.

Measures Overview: We have selected measures based on 4 criteria: 1) importance for testing our conceptual model, 2) psychometric properties, 3) brevity, and 4) demonstrated validity in BD and SZ studies. Participants will be assessed at Baseline, 6 weeks, 12 weeks and 24 weeks.

We propose to add several measures to the protocol as detailed below.

Summary of Measures (Total estimated time= 4 hours baseline; 2.5 hours follow up):

Table 1. Summary of Measures in Original and Supplement

Measure	Specific Aim	Construct Assessed	Time (Min.)
PARENT STUDY			
MINI	Inc/Aim 3 (Moderator)	Diagnosis	25
Demographics, Meds	Descriptive	Sample Characterization	15
BPRS	Aim 1 (Primary)	Global Psychopathology	15
EMA Outcomes	Aim 2 (Secondary)	Mood/psychotic symptom severity, medication adherence, socialization	Various

Tablet Routine Quest.	Aim 2 (Secondary)	Self-reported medication adherence	2
Pharm. Record Adherence	Aim 2 (Secondary)	Objective medication adherence	--
Social Functioning Scale	Aim 2 (Secondary)	Social functioning	30
PSR Toolkit	Aim 2 (Secondary)	Objective real-world function	--
MCCB (Baseline Only)	Aim 3 (Moderator)	Cognitive Impairment	60
Beck Cog. Insight Scale	Aim 3 (Mediator)	Self-reflectiveness and evaluation	10
Dysfunc. Attitudes Scale	Aim 3 (Mediator)	Maladaptive attitudes	10
Columbia Suic. Severity	Safety	Suicidal ideation and behavior	10
NEW MEASURES FROM SUPPLEMENT			
Scale for Suicidal Ideation	Supplement Aim 1,2	Suicidal ideation	10 (B,6,12,24)
Reasons for Living Inventory	Exploratory	Deterrents to Suicide	10 (B, 12)
Iowa Gambling Task	Supplement Aim 1	Impulsive decision making	15 (B)
UPPS Impulsivity Scale	Supplement Aim 1	Impulsive traits	15 (B)
ER40	Supplement Aim 1	Social emotion recognition	5 (B,12)
Interpersonal Needs Ques.	Supplement Aim 1	Social beliefs related to suicide risk	5 (B,12)

Diagnosis and Background Characteristics: Diagnosis will be obtained by administering the Mini-International Neuropsychiatric Inventory (MINI)[28], rather than the more lengthy SCID.

Global Psychopathology (Primary Outcome): The primary outcome will be the Brief Psychiatric Rating Scale – 24 item expanded version 4.0 (BPRS-24)[29]. The BPRS-24 is a clinician rated measure that includes 24 items that cover depression, anxiety, mania, suicidality, delusions/hallucinations, and unusual behavior.

EMA Measures of Symptoms, Medication Adherence, and Socialization (Secondary Outcome): EMA ratings are single-item, thrice daily 1-7 scales (1 “not at all” to 7 “extremely”) for severity of depression, voices, and mania, along with medication adherence (binary yes or no response) and socialization (number of social interactions).

Beck Anxiety Inventory (Secondary Outcome): The BAI is a 21-item self-report inventory rated on a scale from 0 to 3. This will allow us to determine how the subject has been feeling in the last month in terms of severity of anxiety. Each item is related to subjective, somatic, or panic-related symptoms of anxiety and the responses range from “not at all” to “severely”[30]

Medication Adherence (Secondary Outcome): **Self-report**: The Medication Adherence Rating Scale[31] will be used, which asks about the willingness and ability to take your medications every day. It has been used to measure medication adherence in psychosis[32,33]

Social Functioning Scale (Secondary Outcome): We will assess social function with the Birchwood Social Functioning Scale (SFS)[34], a 79-item self-report of social functioning across 7 domains: 1) social engagement, 2) interpersonal behavior, 3) prosocial activities, 4) recreation, 5) independence/competence, 6) independence/performance, and 7) employment. The SFS is

administered in interview (versus self-report) and best estimate ratings are based on observations

Specific Levels of Functioning Scale (Secondary Outcome): The SLOF is a multidimensional behavioral survey administered to the caseworker or caregiver of a patient with schizophrenia[35]. The scale assesses the patient's current functioning and behavior across six different domains. We will be looking at only 4 of them: Interpersonal Relationships, Social Acceptability, Activities of Community Living, and Work Skills. Each of these questions is rated on a 5-point Likert scale. The lower the total score means the better overall functioning of the patient.

PSR Toolkit (Secondary Outcome): The PSR Toolkit[36] is used to collect objective information on employment, residential situation, and hospitalizations/ER visits. The measure requires no subject testing burden, because research staff complete the PSR Toolkit (with participant release of information) by obtaining medical records, employment status records, visiting residential settings to determine level of services (With release of information for each of these obtained).

Columbia-Suicide Severity Rating Scale (Secondary Outcome): The C-SSRS is a semi-structured interview used to measure both behavior and ideation of suicidality[37]. It is evidence-based, and well-supported.

Cognitive ability (Moderator, Baseline only): Cognitive ability will be measured with the MATRICS Consensus Cognitive Battery (MCCB) developed through systematic selection and psychometric evaluation of the tests involved[38].

5 Choice-Continuous Performance Task (5C-CPT): The 5C-CPT is a computer task of sustained attention and response inhibition that was developed based on a rodent paradigm.

Suicide Related Phenotypes: As noted above, we already administer the Columbia Suicide Severity Rating Scale (CSSRS) Lifetime (baseline) and Interval assessments (follow-ups). The CSSRS is part of the PhenX Suicide Specialty Collection. The CSSRS provides indices related to active ideation and behavior, but we lack more subtle measures of ideation or protective factors. The SSI will be the primary dependent variable for Supplement Aims 1 and 2.

- **Scale for Suicidal Ideation[16] (Baseline, 6, 12, 24):** The Scale for Suicide Ideation (SSI) is a 21-item, interviewer-administered scale assessing intensity attitudes, behaviors, and plans to commit suicide on the day of the interview. This scale will provide additional continuous information about the intensity of current ideation beyond that already collected in the CSSRS. We will omit the final 2 questions that concern historical attempts, because that information is already gathered by the CSSRS. The SSI is a recommended measure from the Suicide Specialty Collection of the PhenX toolkit.
- **Deterrents to Suicide (Baseline and 12 weeks):** The Reasons for Living (RFL)[17] inventory is a 48 item self-report measure of potential reasons for living versus attempting or committing suicide. Subscales include coping, family and children, fear of suicide, social disapproval and moral objection. The scale is also included in the PhenX toolkit. The total score will be used for analyses and exploratory analyses will examine subscales (particularly beliefs about social disapproval or the absence thereof)

Impulsivity Related Phenotypes: We will include, for Aim 1, both behavioral and additional self-report measures for impulsivity. These are:

- **Iowa Gambling Task (Baseline Only):** The Iowa Gambling Task[18,19] is the most commonly administered behavioral task of impulsive decision making and is part of the PhenX Toolkit. It is a computer-administered task involving strategy in decision making yielding indices that represent advantageous and disadvantageous decisions in a simulated gambling paradigm. The total score is the difference between the number of advantageous and disadvantageous choices. A number of studies have linked aberrant performance to suicide-related phenotypes[20], as well as impairment in performance compared to normal controls in SMI[21]. Due to practice effects, the IGT will only be administered at baseline.
- **UPPS (Baseline only):** The UPPS Impulsive Behavior Scale[22] contains 59 self-administered questions that are scored as five subscales (urgency, premeditation, perseverance, sensation seeking, and positive urgency). The UPPS is widely used in the study of adult psychopathology and has been

previously associated with increased risk of suicidal behavior, in particular lack of premeditation and positive urgency in the presence of negative affect[23]. The choice of the UPPS over other measures of impulsivity (Barratt impulsivity scale) reflected our desire to measure multiple sub-constructs of impulsivity in relationship to suicide risk, given prior work identifying differentiation among constructs in sucidality. We will use the total score as the primary predictor. As the UPPS reflects trait-like aspects of impulsivity, it will only be administered at baseline.

Social Threat Related Phenotypes: We will include, for Aim 1, both behavioral and additional self-report measures for social threat. These are:

- **ER40 The Penn Emotion Recognition Task (Baseline, 12 weeks).** The ER40[24] is a measure of emotion recognition. It is comprised of 40 photographs of actors expressing one of four basic emotions (happiness, sadness, anger, fear) or a neutral expression. Photos are presented in a random order, and participants are asked to identify the emotion expressed by each face, and both the response and response time are recorded. The primary outcome is the number of correct responses. The ER40 was selected as a high performing measure with strong reliability, tolerability and concurrent validity with functional outcome in a recent psychometric study of social cognition in schizophrenia (SCOPES study)[25]. We will examine the tendency to over attribute anger to neutral faces as in previous studies[26].
- **Interpersonal Needs Questionnaire[27] (Baseline, 12 weeks):** The INQ measures key constructs in the Interpersonal Psychological Theory of Suicide. There are two subcales, Thwarted Belongingness and Feeling of Burdensomeness. Of particular import to the proposed study, Thwarted Belongingness represents the tendency to feel alienated from others and society. Based on our preliminary data, our hypothesis is that social alienation is associated with suicidal ideation in psychopathology associated with schizophrenia. Based on prior work comparing versions of the INQ, we opted to use the 15-item version of the INQ based on the strengths of its psychometric properties[28]. The total score on the Thwarted Belongingness subscale will be used.

Mediators: Our two mediators, cognitive insight and negative performance beliefs, will be measured with the Beck Cognitive Insight Scale (BCIS) and Dysfunctional Attitudes Scale (DAS, Form A, both self-report scales.

Satisfaction Questionnaire (12 week only): Participants in the CBT2go and EMA-only conditions will complete seven 5-point Likert-type and 4 open-ended questions (modified from Kimhy and colleagues[39] and used in our prior research[40]) about experiences with the device and suggestions for future usability.

Quality Assurance: The PI will train and supervise raters by reviewing videotapes of interviews. Consistency between raters will be established prior to data collection using gold standard videos, with a standard inter-rater agreement of 0.80. Checks of inter-rater reliability will be conducted semi-annually thereafter. To preserve the blinding of the study and minimize rater bias, raters will not be involved in the treatment. Participants will also be instructed not to disclose their treatment assignment during assessments. If such disclosure is made, the rater will stop the assessment and another rater will continue the assessment.

Intervention Procedures (CBT2go, EMA-Only, and Standard Care Conditions):

Device: As in previous trials, we will use the touch-screen Samsung Fascinate, a 4G Android OS smartphone. These devices will have a data plan (and can receive incoming calls). We will provide this device to participants. Participants will be informed that if they lose or damage the device they will not be held responsible.

Device Training: Device training covers how to operate the device, the meaning of all questions and response choices, and procedures for carrying the device and responding to alarms. Participants will also be trained in how to access and use crisis lines. This session will be individually-tailored to the learning needs of each participant, until participants can complete a trial run and feels

comfortable with the device. The Project Therapist or PI will be available to answer questions every day.

EMA Protocol: Interactions are triggered by a text message sent via an SMS gateway (with a "shortcode" referenced to our study), which automatically opens the browser wrapper that displays questions and alerts participants with vibration or ringtone. The timing can be adjusted to accommodate each participant's preferences (e.g., sleep and wake schedules) and alarms can be silenced for 30-minute intervals (e.g., during driving). All data entries will be time stamped and responses recorded in real time. Data are accessible at all times only to study staff on a password protected server. If participants stop responding before the end of the questions, the data are still recorded; participants cannot "backfill" surveys as they expire in 15 minutes of the terminal alarm. Labeled on the back of the device is the investigator contact information and crisis line information. Participants will be instructed to answer the surveys and then return with the device at Week 12.

EMA Questions: Participants will respond to surveys three times per day for 12 weeks. The frequency (3 times per day, morning, mid-day, evening) and timing (random initiation at approximately 2 hour intervals) of EMA surveys are based on preliminary data described above. In each of morning, mid-day, and evening surveys, participants will be prompted to answer multiple-choice questions (i.e., they do NOT type in answers) asking: What are you doing? (e.g., working, non-physical leisure), Who are you with? (e.g., alone, with family), Where are you? (e.g., at home, at work), and 7-point Likert scales are used to rate mood and symptoms (e.g., Are you sad? "Not at all" to "Extremely" or Have you been bothered by voices? "No voices" to "Extremely"). They also report whether or not they have taken prescribed medications and the number of social interactions since the last signal. The format of these questions is identical between EMA-only and CBT2go.

GPS Data: In addition to sending surveys, the device will be collecting data on the location of the participant via GPS. Our purpose in collecting this data is to provide a proxy measure of physical activity which we hypothesize will be correlated with self-reported mood and activity ratings. If our results are consistent with this hypothesis, there is considerable potential benefit to future mobile health care programs in reducing participant burden of manually providing self-report data, if unobtrusively gathered data on location can serve as a suitable proxy. The data, which are geographic coordinates, are encrypted (base 64 encryption) so that the potential for breach of confidentiality is minimized. The data are de-identified and not stored on the local device and so therefore cannot be accessed should the device be lost or misplaced. This de-identified data and kept in a file separate from other self-reported data in a locked location in a password-protected computer. Once we calculate the distance between coordinates obtained, we will erase the data on the specific coordinates prior to merging these data with other self-reported data. This process mitigates any possibility that individuals could be identified through specific coordinates in case the unlikely event that there is a breach of confidentiality of stored data. Participants have the option to refuse this action during the consent process and at any time thereafter if they elect to stop this form of data collection by notifying the investigator or research staff.

EMA-only Single In-Person Session: To match the EMA-only and CBT2go conditions for therapist contact, after device training at baseline, participants in the EMA-only condition will receive standard psychoeducation about their mental illness (reviewing NIMH patient educational material) and instructions in accessing community crisis lines and related resources in a single individual in-person meeting for one hour and will receive telephone contact every two weeks to troubleshoot device operation.

A subset of 30 Bipolar participants in the EMA-only condition who indicate interest on their consent form (see below) will be approached about obtaining a total of 3 blood draws and cognitive assessments over the first two weeks of the study by participating in two additional encounters. During their in-person session, these participants will undergo the consenting process for these additional procedures, and if they agree to participate, they will immediately be administered the 5 Choice Continuous Performance test of attention and have 5 ml of blood drawn by a trained phlebotomist on staff. Blood pressure will also be measured. This will add one hour to the in-person session for eligible and willing participants. On day 7 (plus or minus 2 days if necessary for scheduling) **Home Visit 1** will occur in the participant's home. A phlebotomist will draw a blood sample of 5 ml, obtain a blood pressure measurement, and administer the 5 choice continuous performance task and digit symbol coding subtest from the MCCB battery. To assess for suicidal ideation, participants will be asked to complete the Columbia Suicide Severity Rating scale. Home Visit 1 is estimated to last 1 hour. On day 14 (plus or minus 2 days if necessary for scheduling) **Home Visit 2** will occur with the same assessments as Home Visit 1. Home Visit 2 is estimated to last 1 hour.

CBT2go Condition, Single In-Person Session: After device training, participants in the CBT2go condition will participate in a single individual in-person meeting for one hour of contact. These sessions will be conducted individually by a Master's level clinician trained and supervised as detailed in below. In this session, education about the generic cognitive model (i.e., that thoughts, feelings and behaviors are related) is provided, thoughts and feelings are identified and labeled, and patients complete exercises demonstrating how dysfunctional beliefs can impact feelings and behavior (e.g., that "Nobody would want to talk to me" leads to sadness and isolation). The notion that correcting mistakes in thinking can change undesirable feelings and behaviors to more adaptive outcomes is introduced. This session includes a structured interview that elicits unhelpful and helpful beliefs associated with mood and psychotic symptoms, medication adherence, and social activities. Evidence used to challenge unhelpful beliefs is garnered ("You said depression always goes away eventually"), as well as a behavioral experiments that can be employed ("Try ignoring the voices and keep track of how you feel"). Participants provide at least three benefits of taking medications and socializing, and at least three coping strategies for depression, manic symptoms, or voices (if present). This information is used to create personalized thought-challenging messages ("But you said taking medications helps you to [personalized benefit]"). For Relapse Prevention, participants identify at least 3 illness triggers or early warning signs of illness exacerbations and form implementation intention statements around these – these are simple "if-then" statements that specify a thought or action that can be taken and the benefit of doing so ("If my mother starts to stress me, then I will take a walk outside so I can avoid an argument"). These statements are programmed to the device from a secure website and used in the automated CBT2go interventions.

CBT2go Condition, Automated Interventions: In CBT2go, responses to surveys branch to intervention content with a focus on challenging dysfunctional beliefs. For instance, if a patient reports that s/he missed a medication dose because "medication is not helpful", a personalized message is presented that challenges accuracy of this belief and the consistency of the non-adherence behavior with previously established values ("*You said taking your medication has helped improve your sleep before and that you valued getting a good night's rest*"). Similarly, if a patient reports that auditory hallucinations cannot be controlled, personalized contradictory evidence to challenge the belief is presented *("But talking with your mother has quieted your voices in the past.*"). Moreover, for illness triggers that have been identified, "if-then" statements provide strategies that were successful in the past *("when you've felt lonely, it helped to take the dog for a walk"*). Patients are also reinforced by the mobile device for endorsing freedom from symptoms for when describing

positive states (e.g., *"What is helping?").*

Technical and Follow-Up Support (EMA-only and CBT2go): Participants will be contacted by phone in the first week after receiving the device and thereafter every two weeks to briefly check in (target 10 minutes) about their experience with the device. Although this contact is minimal, substantial research suggests human oversight of technology-based interventions is associated with greater adherence and efficacy[41-43]. In case of crises (see Human Subjects for safety precautions) or difficulties with the device, participants can notify Project Manager or PI through the device, and a log will be kept of all ad-hoc contacts. Participants can obtain a new device at no cost in case of malfunction or loss.

Standard Care Condition: Participants will not be provided with a device or receive any study interventions, but will receive all study assessments and continue to participate in all ongoing treatments in the community. As seen Human Subjects, participants in crisis will be evaluated and referred to services.

Intervention Fidelity: We will address the relevant components of Treatment Integrity: Competence, Therapist and Participant Adherence, and Treatment Differentiation[43]. Competence will be addressed by requiring the Project Therapist to have at least a Master's level of training, previous clinical experience with SMI, and attend a full day training on the intervention by Drs Depp, Perivoliotis, and Granholm. Therapist Adherence to the manualized protocol will be assessed via audiotapes, supervision, and submitted checklists measuring conformance to session content. Therapist adherence will be monitored by Dr. Perivoliotis via audiotape for 25% of randomly-selected participants on an ongoing basis. Participant adherence is assessed objectively via device obtained data. Treatment Differentiation is assessed by blinded random selection of 25% of audiotapes 2/year and ratings by Dr. Depp the conformance of sessions to condition assigned. Any observed carry-over effects result in ad-hoc retraining in the elements of each of the active conditions. Participants will be asked to sign a separate consent to have these contacts audiotaped. Participants can still participate in the study if they elect not to be audiotaped.

Intervention Fidelity: We will address the relevant components of Treatment Integrity: Competence, Therapist and Participant Adherence, and Treatment Differentiation[43]. Competence will be addressed

10. HUMAN SUBJECTS

We will recruit 255 participants in the according to the table below, with Year 5 for completing interventions, follow-up assessments, and the implementation component of the project.

Recruitment Goals and Number of Contacts (i.e., Intervention and Assessments)					
	Year 1	*Year 2*	*Year 3*	*Year 4*	*Year 5*
CBT2go Intervention Condition	15	23	24	23	0
EMA-Only Condition	15	23	24	23	0
Standard Care Condition	15	23	24	23	0
Total In-Person Contacts/year	180	276	288	276	138

Complete Inclusion/Exclusion Criteria are as follows:
Participants in this study will be included if: male or female, any race/ethnicity and age 18-65; have a DSM-IV-TR diagnosis of BD, SZ, or schizoaffective disorder based on the MINI; minimum level of impairment on at least one of the target outcomes, defined as a score of ≥ 3 on the BPRS depression, mania, hallucinatory behavior, or asociality items; current outpatient participation in

routine psychiatric care and on stable medications, defined as the same regimen for at least 60 days and a constant therapeutic dose for at least 30 days; willing to sign a release of information form in order for study staff to be able to inform treating clinicians of symptom exacerbations/suicidality; able to speak and read English ; and capable of and willing to provide signed informed consent and pass the UBACC test for decisional capacity for research (see below).
Participants will be excluded if: diagnosis of dementia or past head trauma with loss of consciousness for > than 30 minutes; cannot complete the assessment battery; visual acuity (assessed with Snellen chart) and manual dexterity sufficient to navigate a touch screen device.

INCLUSION OF WOMEN AND MINORITIES

According to the 2010 US Census, for adults in San Diego County, 47% were male and 71% were Caucasian. We will strive to achieve a similar sample composition, so that the data will generalize to the larger population. In our preliminary studies, the proportion of patients who identified as Caucasian was 72% and the proportion of men was 52%. Notably, our sample ascertainment for the proposed study will be more likely to include members of ethnic minorities, as we will be recruiting directly and exclusively from the San Diego County Mental Health System. As described in a recent Annual Report of San Diego County Mental Health (viewable at http://www.sdcounty.ca.gov/hhsa/programs/bhs/documents/AMHS_0809.pdf), a total of 48% of system users were members of ethnic minority groups (Hispanic/Latino, 19%; African-American, 12%). The gender distribution of San Diego County Mental Health users was evenly divided among men and women. Therefore, we anticipate being able to recruit an ethnically diverse sample with equal proportions of men and women. Neither gender nor ethnicity will be a criterion for inclusion or exclusion of subjects. We will continuously monitor the gender distribution for this study, as well as the ethnicity characteristics of the sample as it accrues. We will keep all research assistants and referral sources informed regarding our progress and our current priorities for recruitment of women and minorities. Thus, we plan to have an ongoing process through which we ensure that women and minorities are included and appropriately represented.

INCLUSION OF CHILDREN

We will include children between the ages of 18 and 21. Patients younger than 18 will not be included, since the use of such subjects would require modification of the neuropsychological battery, psychiatric interview and functional assessments, thereby substantially changing the research design. Further, the functional abilities of individuals under the age of 18 tend to be different than those of adults and expectations regarding the type and nature of social interactions, independent living, and financial self-support are notably different under the age of 18.

11. RECRUITMENT

Recruitment of participants and informed consent procedures will follow established methods in previous ACISIR studies. The referral sources for this study will be the clinics and other outpatient service sites of the San Diego County Adult and Older Adult Mental Health System (AOAMHS), which serves over 43,000 persons per year (see Resources). Our recruitment efforts will include community clinics with mental health clinics throughout the San Diego County AOAMHS that serve primarily Hispanic and African American populations. Participants will be recruited by a variety of methods, including direct referrals from providers, posted flyers and informative brochures, staff in-services and community outreach meetings. These recruitment methods have been honed in our long-standing academic-community partnership with the San Diego County Mental Health System as described in our previous publications[44-46]

Upon contact with staff, potential participants will undergo a brief telephone screening interview (or in-person in rare cases), during which the Project Manager will introduce the study and review the inclusion/exclusion criteria and study procedures. If the participant is appropriate for inclusion into the study and interested in participation, a staff member will describe the requirements of the study, including questionnaires, assessments, and randomization to interventions. In all cases, fully informed consent will be obtained and Dr. Depp and other co-investigators will be directly available to answer questions, should any be raised by the participant.

BD participants who have been randomized to the EMA-only condition who have indicated on their consent that they are willing to learn about participating in additional procedures (blood draws and home visits for the first 2 weeks) will be approached at their single in-person session to undergo the consent process for these assessments.

12. INFORMED CONSENT

Individuals are provided with a copy of the consent document and a copy of the Experimental Subject's Bill of Rights. Potential participants are encouraged to ask questions throughout this process. Those who are eligible are fully informed and consented for the full study and provided with a copy of that consent documentation. All research subjects are informed regarding applicable HIPAA protections and sign a separate HIPAA document. To enhance comprehension, the informed consent documents are written at the 8th grade level of language. All participants will informed of the possibility of additional compensated procedures for an eligible subset of participants, and will be asked to indicate their interest in learning about these home visits and blood draws (described above).Informed consent will be documented with the IRB-approved written consent form that each participant will sign prior to participation. Signed and witnessed consent forms will be kept on file in a specially secured cabinet.

Our screening protocol contains a direct assessment of decisional capacity, in light of the elevated base rate of cognitive impairment among participants with bipolar disorder or schizophrenia that can lead to diminished capacity to understand, appreciate, and apply sound reasoning in the decision to participate in research. In order to ensure that all participants have adequate decisional capacity to participate in this research study, we will administer the University of California San Diego Brief Assessment of Capacity to Consent (UBACC)[29], which is a 10-item questionnaire that is tailored to the specific procedures of the study. This measure queries participants about the basic procedures, risks, benefits, and purpose of the study, along with participant rights.

If a potential participant is unable to achieve a perfect score on the first or second administration of the quiz or if there is any other reason to suspect that the individual may lack the capacity to give informed consent because of decisional impairment, that individual is assessed by a study clinician. The final determination regarding decision-making capacity is made by the clinician and documented in the research record. If an individual is unable to demonstrate the capacity to consent as detailed above, the individual will be excluded from the present study.

13. ALTERNATIVES TO STUDY PARTICIPATION

Participating in the study will not alter participant's care. For participants who are interested we will provide referrals to them for community mental health providers and the free depression bipolar support group held weekly at the VA Hospital. Alternative to study participation is to not participate in this study.

14. POTENTIAL RISKS

Assessment: The interviews, questionnaires, computer-based assessments, and neuropsychological tests are non-invasive clinical assessments associated with minimal risk. All measures are physically non-invasive, have been used in prior studies with seriously mentally ill participants, and have been found to elicit minimal distress and discomfort. Nevertheless, participation in the psychosocial evaluation and responding to questions on the mobile device will require time and attention. Some participants may become bored or fatigued completing the evaluation. Some participants may also become distressed during the psychiatric evaluation, which requires them to discuss their current symptoms, as well as the history of their symptoms.

Intervention: Risks involved in participating in this intervention are minimal. During the Baseline assessment and follow-up assessments, participants may experience feelings of anxiety or discomfort while talking about themselves and/or symptoms. Participants may also become fatigued by filling out questionnaires or answering questions in person, or, if they are randomized to the experimental conditions that involve mobile devices, on the device.

Confidentiality: As with any intervention study, a risk of disclosure of personal material exists.

Blood Draw: A subset of interested subjects in the EMA-only condition will be asked to give 3 blood samples over the course of their participation. For most individuals, needle punctures for blood draws do not cause any serious problems. However, there is a small risk of bleeding, bruising, discomfort, infections and/or pain at the needle site or dizziness.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Assessment: During in-person interviews, trained raters will closely monitor for signs of stress, fatigue, and distress. Rest breaks will be provided as needed during all assessments to reduce fatigue and boredom. Also, subjects may refuse to answer any specific questions or to complete any given tests. We provide snacks, water and recommend breaks to participants if they report feeling fatigue. We also provide participants the option of splitting the assessments, particularly the baseline assessment which is longer than the other assessments, on different days. They will also be advised that they can withdraw from the study at any point and can still receive the compensation. If a participant discloses that he or she is experiencing suicidal ideation during diagnostic interviewing or on standard clinical measures, the rater will immediately contact the PI to ensure that steps are taken to ensure the participant's safety. The two measures that directly elicit information about current suicidal thoughts are the Columbia Suicide Severity Rating Scale and the Scale for Suicide Ideation. Any report of ideation on these instruments that exceeds "none" will result in an immediate contact to the PI to ensure participant safety. These steps will include a formal risk assessment and may lead to contacting the participant's providers (with signed consent to do so) and arranging emergency care for the participant. Our research center has a Clinical Response Team (of which the PI is the Associate Director) that will provide additional back-up; this team includes board-certified psychiatrists and psychologists who will are available and on site at all times.

In-Person Session (CBT2go): The Project Therapist will receive intensive training from supervising psychologists and will be provided supervision on a weekly basis by Dr. Perivoliotis. Participants will be closely monitored and additional (in session) assistance will be provided to those participants experiencing frustration or distress. Should a participant be observed to be exhibiting an acute symptom exacerbation and/or suicidal or homicidal ideation, the Project Therapist member will notify Drs. Perivoliotis or Depp immediately and they will conduct a formal evaluation of the participant with

additional back-up from the Clinical Response Team. Given that all participants must be currently participating in stable outpatient care, the need for immediate emergency services will be unlikely. Nevertheless, based on our experience conducting clinical research in serious mental illness, we have developed the above plan to intervene appropriately should such a need arise.

Experimental Conditions (Week 1 through Week 12): Participants in the CBT2go and EMA-only conditions will be provided a smart-phone device with which to answer questions about their mood, activities and contexts. After baseline interview (and in-person session if in the CBT2go condition), participants will be asked to respond to questionnaires on the device until Week 12. Participants in the Standard Care condition will not be provided a device. We have taken several steps to ensure participant safety during the periods of no in-person contact. All participants will be provided with staff contact information and emergency resources in a printed manual, and they will be instructed that they may call the PI or project manager at any time in case of questions or emergencies. Participants must provide release of information for our staff to contact treating psychiatrists or other appropriate healthcare provider, so any emergent crises will be relayed to that participant's provider. In the CBT2go and EMA-only condition, responses at the severe spectrum of the mood or voices scales are accompanied with a screen that instructs participants to contact both emergency services (911 can be directly accessed via the device) AND project staff, if in crisis. We will monitor these protocols during the course of the study and will make adjustments to inclusion/exclusion criteria in case of adverse events.

Data and Safety Monitoring Board: The study will be reviewed annually through the UCSD DSMB. The board consists of non-UCSD faculty in psychiatry, community members, and bioethicists.

Blood Draw: Blood samples will be drawn only by research staff trained and certified in phlebotomy. Staff will take care to assure the participant is comfortable and participants will be provided with the necessary medical equipment (e.g. band-aids) to care for any irritation at the site of the blood draw.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Confidentiality: In order to protect confidentiality, all participant data will be de-identified by assigning each participant a unique ID in computer files, and all physical files from the study will be kept in a locked cabinet in our offices at the Stein Clinical Research Building at UCSD. All electronic data and files will be stored on a secure server. Only study investigators and personnel will have access to these data. All documentation will identify participants only by their Unique ID number and not other personally identifying information.

On the device, participant data is not stored locally and cannot be accessed by anyone if the device is lost or stolen. Data are encrypted upon transfer to our server and linked by unique ID that is de-identified. Since we will be providing the devices to participants, there is no risk of loss of confidentiality associated with access to personal telephone numbers. Should the participants lose the device, we have taken the additional step of incorporating the Auto wipe application on all study deices which enables remote factory reset of the device, erasing all data. If participants lose or damage the device, they will not be held responsible for the cost of the device or any other costs.

Data and Safety Monitoring Plan

Data safety will be of utmost importance in this project. Data will be coded by subject number only and will be filed in locked file cabinets in locked staff offices. In addition, signed consent forms will be filed in a separate location from the raw data. A codebook linking subject identifying information with

subject number will be kept on a computer that is password protected and, within that, a file that is password protected.

Adverse events in this research project are expected to be extremely rare. However, we have established plans for resolving any adverse event should one occur. First, during screening for the project, trained research personnel will assess (using standardized screening tools) for any serious medical or psychological conditions that may require immediate medical attention or psychiatric treatment. The rationale for this is because the presence of serious medical or psychiatric conditions would make these individuals inappropriate for the proposed research study. Should attention be required, staff will provide these individuals with information about suitable referrals, including local hospitals, clinics, and/or relevant health-care and mental health professionals, and they will strongly encourage the individuals to follow up with these referrals.

Second, UCSD's IRB requires regular updates on the status of research projects, including the number of participants enrolled, adverse events or unanticipated problems, number of withdrawals from the project, complaints about the research, and any protocol changes. The IRB also monitors the consent forms and ensures that appropriate HIPAA information is included.

Third, the Data and Safety Monitoring Board of the Research Center will review the project yearly.

Taken together, use of these methods should allow for adequate evaluation of, and response to, both potential enrollees and actual participants.

17. POTENTIAL BENEFITS

As these are experimental interventions, there may be no direct benefit to participants. However, benefits to the individual participants may include decreased emotional distress and improved functioning from cognitive and behavioral changes facilitated by the interventions. Participants may gain an increased understanding of the role thoughts and behaviors play in the symptoms of schizophrenia or bipolar disorder and may learn to reduce their symptoms by changing these thoughts and behaviors.

18. RISK/BENEFIT RATIO

The risks of this proposal are minimal. Protection of subject confidentiality and privacy are rigorously guarded by the assignment of coded numbers to each subject's data. Keys to these codes are stored in a locked file cabinet in the Stein Clinical Research Building. The dangers of adverse effects associated with this intervention are minimal. The benefits to the individual participants may be minimal, but may include decreased emotional distress from behavioral changes that they achieve. We judge the importance of knowledge resulting from this study and the potential for maximizing independence among psychiatrically stable individuals with bipolar disorder or schizophrenia to be quite significant; therefore, the risk to benefit ratio is low.

19. EXPENSE TO PARTICIPANT

There are no expenses to the participants. Participants will not be asked to pay for the device if it is lost or broken.

20. COMPENSATION FOR PARTICIPATION

Patients will be assessed (4-hour battery) at baseline, and a 2.5 hour testing battery at mid-point (6 weeks), post-treatment (12 weeks) and 3-month follow up (24 weeks) and paid $70 for each assessment (there is no payment for treatment participation).

Participants will be provided a total of $330 for completing all assessments – the compensation

structure is graded such that a $50 bonus is provided for returning the device or attending all of the assessments. If the participant elects to drop out of the study, s/he will be offered the opportunity to return the equipment and complete assessment for $50 compensation and will be notified that the mobile device will be deactivated remotely.

The SLOF questionnaire has three versions which are completed by the interviewer, the participant, and an informant of the participant. We will be providing informants with a small gift for completing the SLOF at each visit (baseline, 6 week, 12 week, and 24 week follow up). The gift will most likely be a small box of chocolates or some sort of snack valued less than 5 dollars

Those BD participants in EMA-only group who agree to participate in additional cognitive testing and blood draws over a 2 week period will be compensated an additional $150.00. They will receive $40.00 at the baseline visit, $40.00 at home visit 1 and the remaining $70.00 at home visit 2.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Colin A. Depp, Ph.D.: UCSD Dept. of Psychiatry. Dr. Depp is a researcher in the department of psychiatry and is a licensed clinical psychologist with clinical privileges at UCSD Medical Center and the San Diego VA.

Eric Granholm, Ph. D., UCSD Dept. of Psychiatry. Dr. Granholm is a researcher in the department of psychiatry and is a licensed clinical psychologist.

Dimitri Perivoliotis, Ph.D. UCSD Dept. of Psychiatry. Dr. Perivoliotis is a researcher in the department of psychiatry and is a licensed clinical psychologist.

Wes Thompson, Ph.D. UCSD Dept. of Psychiatry. Dr Thompson is an assistant professor in the department of psychiatry and a statistician.

Lisa T. Eyler, Ph.D. UCSD Dept. of Psychiatry. Dr. Eyler is a researcher in the department of psychiatry and is a licensed clinical psychologist.

Cris Achim, Ph.D., UCSD Dept. of Psychiatry. Dr. Achim is a researcher in the department of psychiatry and will oversee the processing of collected blood samples.

Benchawanna Soontornniyomkij, Ph.D., UCSD Dept. of Psychiatry. Dr. Soontornniyomkij is a researcher in the department of psychiatry and will be conducting the blood assays.

Dilip V. Jeste, M.D. UCSD Dept. of Psychiatry. Dr. Jeste is a researcher in the department of psychiatry, as well as California licensed and board certified geriatric psychiatrist**.**

Jason Holden, Ph.D.: Project Coordinator

Rosa Gutierrez, B.A.: Psychometrist

Mary Linges: Psychometrist

Jennifer Villa, Student Assistant, will be providing general lab assistance. She will also be trained in administering assessments and help staff with contacting participants.

Shirleen Cheng, trained and licensed phlebotomist, will administer informed consent, administer clinical and cognitive assessments, and perform blood draws to a subset of BD participants.

Sheena Dev, B.S., and Ashley N. Sutherland, M.A., will be involved in consenting and administering clinical and cognitive assessments to the subset of 30 BD subjects who elect to participate in the blood draws.

Savannah Raye, Student Assistant, will be providing general lab assistance, such as data entry and other office duties.

Yang Jiao, Student Assistant, will be providing general lab assistance, such as data entry and other office duties.

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23. FUNDING SUPPORT FOR THIS STUDY

NIMH Grant MHR01 100417; NIMH Grant Supplement MH 100417

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

As described above, we will obtain three 5 ml blood samples from a subset of willing BD participants. Blood will be drawn into a blood collection tube and placed in a biohazard container for transportation. The staff phlebotomist will transport the specimen directly to Dr. Cris Achim's laboratory at UCSD immediately after visit completion and the blood samples will be stored at room temperature until assay.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

There is no anticipated impact on staff at UCSD

27. CONFLICT OF INTEREST

None

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

None

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

There will be no surrogate consent obtained in this study.

Our screening protocol contains a direct assessment of decisional capacity, in light of the elevated base rate of cognitive impairment among participants with bipolar disorder or schizophrenia that can lead to diminished capacity to understand, appreciate, and apply sound reasoning in the decision to participate in research. In order to ensure that all participants have adequate decisional capacity to participate in this research study, we will administer the University of California San Diego Brief Assessment of Capacity to Consent (UBACC)[29], which is a 10-item questionnaire that is tailored to the specific procedures of the study. This measure queries participants about the basic procedures, risks, benefits, and purpose of the study, along with participant rights.

If a potential participant is unable to achieve a perfect score on the first or second administration of the quiz or if there is any other reason to suspect that the individual may lack the capacity to give informed consent because of decisional impairment, that individual is assessed by a study clinician. The final determination regarding decision-making capacity is made by the clinician and documented

in the research record. If an individual is unable to demonstrate the capacity to consent as detailed above, the individual will be excluded from the present study.