

Official Title: Targeting a Genetic Mutation in Glycine Metabolism With D-cycloserine (DCS)

NCT number: NCT02304432

Document Date: 4/9/2015

**Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.**

**PRINCIPAL/OVERALL INVESTIGATOR**

Deborah L. Levy, Ph.D.

**PROTOCOL TITLE**

Targeting a Genetic Mutation in Glycine Metabolism with D-cycloserine

**FUNDING**

NIMH

**VERSION DATE**

4/9/2015

**SPECIFIC AIMS**

Concisely state the objectives of the study and the hypothesis being tested.

We propose to (1) to target a triplication of *GLDC* by trying to normalize brain glycine levels using D-cycloserine augmentation of usual psychotropic drug treatment, and (2) to characterize the neurobiology of this mutation using neurocognitive and electrophysiology measures and studies of brain structure and function.

**BACKGROUND AND SIGNIFICANCE**

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Multiple rare structural variants of relatively recent evolutionary origin are recognized as important risk factors for schizophrenia (SZ) and other neurodevelopmental disorders [e.g., autism spectrum disorders, mental retardation, epilepsy with odds ratios as high as 7-30 (Sebat et al. 2009; Malhotra et al. 2011; Heinzen et al. 2010; Weiss et al. 2008; McCarthy et al. 2009)]. We have found a *de novo* structural rearrangement on chromosome 9p24.1. In addition to other genes, the duplicated region contains the gene encoding glycine decarboxylase (*GLDC*), which affects brain glycine (Gly) metabolism. Here we focus on the potential contributions of this gene to abnormal glycine homeostasis and N-methyl-D-aspartate receptor (NMDAR) dysfunction in SZ. This mutation is an obvious ‘smoking gun.’ *GLDC* encodes the glycine decarboxylase or glycine cleavage system P-protein, which is involved in degradation of Gly in glia cells. Carriers of the *GLDC* triplication would be expected to have low levels of brain Gly, resulting in NMDA receptor-mediated hypofunction, which has been strongly implicated in the pathophysiology of SZ (Olney & Farmer, 1995; Coyle, 2006; Javitt, 2007). Individuals with mutations that lower brain Gly or alter other aspects of glutamatergic transmission are obvious candidates for Gly augmentation or complementary NMDAR modulatory strategies, which have been used with varying degrees of success Goff et al. 1999; Javitt et al. 2001; Lane et al. 2005; Heresco-Levy et al. 2004; Buchanan et al. 2007). Genetic risk factors, including variants that impact the synthesis and breakdown of Gly, are likely to contribute to this variability.

## **RESEARCH DESIGN AND METHODS**

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, “Enrollment at Partners will be limited to adults although the sponsor’s protocol is open to both children and adults.”

The total projected sample size is 2, consisting of two carriers of the 9p24.1 mutation, both of whom participated in the protocol entitled Neurobiology of a Mutation in Glycine Metabolism in Psychotic Disorders (2012P001597). The two carriers have diagnoses of bipolar disorder with psychotic features and schizo-affective disorder and will be recruited as outpatients. The age range is 33-64 and includes one male and one female. Inclusion is restricted to these carriers of this specific mutation. This is a private mutation, present only in these two individuals. Exclusion criteria: meeting inclusion criteria but having a creatinine clearance less than 50 mL/min.

### **Design of the study:**

Open-label DCS (daily dose of 50 mg) for 8 weeks – Treatment Arm A, followed by four 6-week periods of double-blind DCS or placebo with one week of washout in between. Subjects will be randomized to DCS-placebo-DCS-placebo or to placebo-DCS-placebo-DCS by the McLean Hospital research pharmacist, Laura Godfrey. These four double-blind exposures (two each for DCS and placebo) will be followed by a 6-week single-blind exposure to DCS (subjects and the person doing the clinical assessments will not know if they are getting DCS or placebo, but Drs. Levy, Bodkin, and Ongur will know that they are getting DCS). After a one-week washout, this single-blind exposure will be followed by 6 weeks of open-label DCS. The length of each double-blind arm is limited to six weeks to minimize the length of symptom exacerbation experienced by the subjects when they are receiving placebo. The patients’ usual psychotropic drug regimen will not be altered as part of the study, but an attempt will be made to keep those medications unchanged throughout the study if possible. Both the DCS (source: The Chao Center) and the placebo will be dispensed by the McLean Hospital Pharmacy. Throughout the study, subjects will take one vitamin-B complex tablet per day.

Dr. Bodkin will be responsible for medical oversight of the d-cycloserine (DCS) augmentation component of the study. Dr. Ongur will serve as his back-up. Dr. Ongur will be responsible for medical oversight of the imaging components of the study.

Briefly describe study procedures. Include any local site restrictions, for example, “Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study.” Describe study endpoints.

Before beginning the study, subjects will have an EKG and physical exam performed by their personal physician. This will be repeated at week 8 and week 44 at the end of the study. Blood work will be done at the same time and consist of the following tests: comprehensive metabolic profile (CMP), lipid panel, GGT, uric acid, CBC with differential, CRP-hs. Blood will also be drawn for large and small amino acid levels and psychotropic drug levels.

Periodic blood tests and weight checks, clinical ratings (PANSS, Clinical Global Impression scale, Brief Psychiatric Rating Scale, Young Mania Rating Scale, HAM-D), side effect monitoring, movement disorder assessments (AIMS and SAS) and neurocognitive testing (MATRICS) – see schema for details.

At the end of week 7 of open-label DCS, subjects will undergo electroretinograms at the University of Minnesota. During week 8 of open-label DCS they will have a structural MRI, Proton <sup>1</sup>H MRS for brain GABA, glutamate, and glycine levels, the MATRICs neurocognitive battery, and an EEG.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Standard care usually does not involve augmentation with DCS. Otherwise, their pharmacological treatment is consistent with the standard of care.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Subjects who meet the inclusion criteria specific above but have a creatinine clearance less than 50 mL/min will be excluded.

DCS Augmentation has been used to augment standard psychotropic drug treatment and is well tolerated. At 50 mg/day, DCS is a partial agonist. It crosses the blood brain barrier readily and should facilitate excitation of the NMDA receptor to compensate for the accelerated degradation of glycine caused by the mutation. Both patients will be taking clozapine; in some patients DCS results in either no clinical effects or a slight worsening of negative symptoms in clozapine-treated patients. The same applies to glycine. The fact that both patients derived considerable clinical benefit from glycine would suggest that DCS should have a similar therapeutic effect. The subjects will be monitored closely by the research team and by their own psychiatrists.

The clinical assessment every two weeks includes an evaluation of suicidality (HAMS and C-SSRS). In addition, there is an at least once-weekly call with Dr. Levy to monitor changes in symptoms. Should any suicidal ideation emerge, Mr. Coleman and Dr. Levy would review the symptoms and their acuteness with Dr. Bodkin (or Dr. Ongur). Dr. Bodkin (or Dr. Ongur) would talk with the subject. We would then have a conference call involving Dr. Levy, Mr. Coleman, and Dr. Bodkin (Dr. Ongur should Dr. Bodkin not be available) to discuss the best disposition: determining whether a subject need to be hospitalized, whether the subject should be discontinued from the study; whether emergency services (911) should be notified. We would confer with the subject's psychiatrist and notify the internist. We would discuss with the subject what we feel is the best plan going forward and facilitate whatever disposition seems best. The subject's family would be informed (with written permission from the subject obtained in the informed consent) to help ensure prompt compliance with the disposition.

The imaging procedures have been used extensively at McLean without complications. Both subjects will be carefully screened again for the safety of the imaging procedures. Both subjects have had multiple brain scans at McLean in the recent past. Baseline imaging data collected in the glycine study will serve as baseline data in this study.

The PI has talked with all of the people involved in the study (Drs. Ongur, Bodkin, Goff, Visscher, Vuckovic; Mr. Coleman, Ms. Godfrey) to ascertain that they are all in agreement that the proposed plan for medical and/or psychiatric monitoring for the patients while they are taking a novel compound is adequate. Dr. Bodkin is the primary medical back-up; Dr. Ongur is back-up

if Dr. Bodkin is unavailable. Dr. Goff is an unpaid consult with expertise in using DCS. Drs. Visscher and Vuckovic are the treating psychiatrists of the subjects. Mr. Coleman performs all clinical assessments. Ms. Godfrey is the research pharmacist.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

#### **FORESEEABLE RISKS AND DISCOMFORTS**

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/Performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The procedures described above pose no serious physical risk to subjects and no psychological, social, or legal risks are anticipated.

Although there are no known general risks associated with MRI scans, there are risks to individual subjects who have contraindications to MRI scanning, including those with metal implants in their body (pacemaker, aneurysm clips, metal screws and plates for orthopedic purposes, hearing implants, certain kinds of tattoos, sheetmetal workers with lodged metal fragments in the eyes). Subjects are screened carefully and excluded if there are even suspected contraindications to scanning. All subjects are asked to remove jewelry, belts and other metal-containing objects. Surgical records will be retrieved prior to scan for subjects who have had metal placed in their body intra-operatively to ensure the hardware is MRI safe, even if the subject has been told the hardware is MRI-safe or if they have had MRI scans since the operation. As an additional precaution, subjects are screened with a handheld metal-detection wand prior to the scan to ensure that no unidentified metal objects remain on the subject. The noise generated by the pulsing of the gradients can lead to temporary decrease in hearing. The use of disposable earplugs is an easy and reliable means of preventing hearing loss. The risks associated with Specific Absorption Rate (SAR) are related to the fact that given a large enough SAR, heating of the tissue may occur. These experiments will comply with all FDA guidelines with regard to RF power deposition. There is also the potential risk of injury from a projectile (i.e., ferromagnetic objects being attracted into the magnet); and of asphyxiation due to large amounts of cryogenic gases generated during a quench (i.e., the event which occurs when a magnet makes the sudden transition from superconducting to resistively conducting). Routine safety procedures are in place at both scanning centers to screen subjects prior to scanning, maintain security of the restricted access areas, and ensure that system security features are in good working order. The McLean imaging center is very experienced with MRI scanning and has an impeccable safety record. The effects of MRI on the fetus are not well characterized, but are irrelevant in this study, because the female patient has had a hysterectomy.

The scans involve use of a standard clinical MRI scanner (3T) as well as a high field (4T) MRI scanner. The 4T scanner is not used for routine clinical studies in children or adults, but the FDA has determined (July 14, 2003) that scanners with magnetic field strengths of less than 8 Tesla do not represent a significant risk to adults, children, or infants older than 1 month.<sup>164</sup> Most people experience no ill effects from 3T or 4 T scans, but some do report claustrophobia, dizziness, mild nausea, headaches, a metallic taste in their mouth, back tingling, double vision,

or sensation of flashing lights. These symptoms, if present, disappear shortly after leaving the scanner. During the scan, the examiner can see and hear the subjects and will ask them to report any problems so the scan can be stopped if necessary. A magnetic resonance scan may be uncomfortable due to claustrophobia, lying still for an hour, or loud sounds. Subjects who express serious concern about these will not be included. The scan will be stopped if the subject expresses discomfort. Total time in the scanner for the structural scan and 2 MRS scans at McLean is 150 minutes, with breaks occurring between scans (structural: 15 minutes; MEGAPRESS: 60 minutes; J-PRESS: 75 minutes). The DCS uptake scan requires multiple scans over a two hour period in the scanner. Subjects will be allowed to leave the scanner between scans and can be re-positioned for the next scan, as described in the application. Both subjects have successfully completed imaging procedures.

DCS Augmentation Clinical Trial: Pharmaceutical grade DCS (The Chao Center) will be used. The dose will be 50 mg/d, which is well within the range of doses that were well tolerated in previous patient studies (Goff et al. 1999a, b, 2005, 2008; Heresco-Levy et al. 1998, 2002). No adverse effects on kidney, liver, hematology or blood chemistry values have been reported. The subjects will be monitored closely by the research team and by their own psychiatrists. Blood chemistries, including liver/kidney function tests, will be monitored at baseline and monthly during the open-label DCS treatment arm as well as every 6 weeks after that. As mentioned above, at the low dose of DCS that we plan to use, the only reported psychiatric side effect was a modest and time-limited worsening of negative symptoms in a small minority of patients who were taking clozapine; this effect may be related to having a high DCS plasma level (Goff et al. 1996, 1999a, b). Interestingly, this mild worsening was not “particularly distressing to patients or clinicians” (Goff et al. 1999a). Subjects will also take one vitamin B-complex tablet/day to ensure that they do not develop B12 and folate deficiency. These are unlikely at the low dose of DCS (50 mg) that will be used.

Periodic blood samples involve the slight discomfort of a needle stick and the small risk of a bruise. Every attempt is made to have the subject feel comfortable and at ease with the environment and the staff. Subjects are debriefed at the end of the day by the study coordinator at which time they can ask questions and express their reactions to the study. Subjects who wish to discontinue the study may withdraw at any time.

Risks to privacy and confidentiality are minimal. All subjects are assigned a random 4-digit ID number, which is used to code all material.

## **EXPECTED BENEFITS**

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, “It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects.” Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

The general goal of this study is to clarify the neurobiology of a mutation in glycine metabolism and to determine whether carriers of this mutation may preferentially benefit from DCS augmentation of their medication regimen. Although subjects receive no immediate benefit from the brain imaging procedures beyond contributing to important research, the potential scientific yield could have a major impact on identifying causal mechanisms in psychotic disorders. If the DCS augmentation is beneficial, these two subjects may experience a significant reduction in psychotic symptoms and improvement in neurocognition, which may also help other subjects

with mutations impacting the glycine metabolic pathway. Since both subjects responded well to glycine, which is a cumbersome to use and an unrealistic long-term treatment, DCS, which is available in a once daily pill would be a helpful long-term clinical adjunct if it is shown to be effective.

## EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The only scientific and ethical justification for including subjects in this study is if their participation can help to clarify the neurobiology of a mutation in glycine metabolism and if they might benefit from DCS augmentation. All other subjects are excluded. Therefore, the only eligible participants at the present time are two carriers of this specific genetic mutation who also have a diagnosis of a psychotic disorder and have participated in the Neurobiology of a Mutation in Glycine Metabolism in Psychotic Disorders (2012P001597) protocol. To our knowledge, this is a private mutation although different mutations in the same gene have been reported in other individuals with psychotic disorders and with autism spectrum disorders. These individuals may be potentially eligible for a similar augmentation intervention.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

N/A

For guidance, refer to the following Partners policy:

Obtaining and Documenting Informed Consent of Subjects who do not Speak English

[https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English\\_Speaking\\_Subjects.1.10.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf)

## RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

The subjects will be selected on the basis of having a triplication of the GLDC gene, a mutation involving an abnormality in glycine metabolism that may be implicated in psychotic disorders, a psychotic disorder, and having participated in the Neurobiology of a Mutation in Glycine Metabolism in Psychotic Disorders (2012P001597) protocol. Prior to beginning the study, the PI will call the subjects and review all of the procedures and time frames. The subjects will be flown to Boston for the McLean procedures and to Minneapolis for the UMN procedures. Other procedures will be carried out in the subjects' city of residence. The procedures will be scheduled well in advance to minimize inconvenience to the subjects and to optimize successful data collection at McLean.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Each subject will be paid \$1,000 for completing the open-label DCS study and \$1,000 for completing the entire double-blind DCS-placebo study. They will each be paid \$200 for the UMN procedures. The imaging, electrophysiology procedures will involve at least 1 week away from work other responsibilities. All expenses incurred as part of participating (e.g., travel, hotel, local transportation, and meal costs) will be paid for by the grant supporting this study. Subjects will be paid a pro-rated amount if unable to complete all procedures based on the proportion of the study that was completed. For example, if a subject completes 80% of the procedures, that subject would be paid \$800. Any additional expenses related to participation, such as gas or taxis, up to \$500.00 in year 1 and up to \$300 in year 2, will be reimbursed based on submitted receipts.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects

[https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment Of Research Subjects.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment%20Of%20Research%20Subjects.pdf)

Guidelines for Advertisements for Recruiting Subjects

[https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines For Advertisements.1.11.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines%20For%20Advertisements.1.11.pdf)

Remuneration for Research Subjects

[https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration for Research Subjects.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration%20for%20Research%20Subjects.pdf)

## CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

The PI and Dr. J. Alexander Bodkin, a licensed physician who provides medical back-up for the study, will obtain written informed consent after reviewing the purposes of the study, detailing the procedures and explaining the informed consent documents. The subjects will have several weeks to consider participation. The subject will be given an opportunity to ask questions after which written informed consent is obtained. Competence to give informed consent will be determined by the PI based on the subject's understanding of the purpose of the study and procedures, what they involve, how long they take, and risk and benefits. The subject receives a copy of the Informed Consent for his/her own files.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as

Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:  
<https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb>

For guidance, refer to the following Partners policy:

Informed Consent of Research Subjects:

[https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed Consent of Research Subjects.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed%20Consent%20of%20Research%20Subjects.pdf)

## DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The scientific integrity of the study and protection of participant safety will be monitored by the investigators using an Adverse Event Tracking Log, including the detection and reporting of adverse events. The safety data include all imaging procedures, the neurocognitive function battery, as well as the double-blind placebo-controlled and open-label DCS augmentation trials. Efficacy data includes all DCS-related procedures.

All adverse events will be promptly reported to the Partners Human Research Committee (PHRC) and NIMH as appropriate. At a minimum, the investigators will review all adverse events at the end of each treatment arm, but more often if needed. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

The research will be altered or stopped if subjects have adverse reactions to any of the procedures (e.g., claustrophobia in the scanners) or significant side effects to DCS. The dose of DCS used in the augmentation trials (50 mg/d) is well tolerated and is a standard dose used in clinical trials. Dr. Goff, a consultant on this project, has a great deal of experience in using DCS to augment the therapeutic effects of antipsychotic medication. Dr. Goff will be available to discuss ongoing clinical states, side effects, and to address any relevant management issues. At least once every week, the subjects will receive a phone call from Dr. Levy to discuss how they are feeling and to review side effects. At the end of the first week of DCS, the subjects will also be called by a study physician (Dr. Bodkin) to assess how they are reacting to the DCS or placebo. Both subjects' psychiatrists will also be monitoring their clinical states and side effects throughout the study. Subjects will be told that if they experience any side effects, they must report them to Dr. Levy or any of the other co-investigators immediately (phone and page numbers through the McLean Hospital operator will be provided).

Partners Collaborative Media (PCM) will provide oversight (for a fee) to ensure that the clinical assessments taking place every two weeks using skype-like video conferencing are secure. Specific web cameras recommended by PCM will be used by McLean staff and by the subjects. All calls will be initiated from McLean using a Partners computer. This computer will have the Cisco program, "movi" [mobile video], installed. PCM will create generic credentials for the subjects such that they will not be using their own actual skype credentials. Thus, if the skype material is stolen, it cannot be linked to the subjects themselves. A McLean clinician will call the subjects by clicking on customized phone numbers and allow the McLean caller to lock the virtual meeting room.

A technical statement about how the secure connection will be implemented has been uploaded.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Subjects will be discontinued from the study if the BPRS shows a 25% worsening or severity of specific symptoms changes by two additional points (compared with baseline). Any adverse events will be immediately reported to the IRB.

## MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The PI will monitor the validity and integrity of the data and ensure that all appropriate forms (e.g., consent forms) have been thoroughly completed and that all blood samples are collected and shipped in accordance with the approved protocol. Monitoring will be done on an ongoing basis in close collaboration with the co-investigators.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance

[https://partnershealthcare-](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf)

[public.sharepoint.com/ClinicalResearch/DSMP\\_in\\_Human\\_Subjects\\_Research.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf)

**Reporting Unanticipated Problems (including Adverse Events)**

[https://partnershealthcare-](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf)

[public.sharepoint.com/ClinicalResearch/Reporting\\_Unanticipated\\_Problems\\_including\\_Adverse\\_Events.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf)

## **PRIVACY AND CONFIDENTIALITY**

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

**NOTE:** Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Each subject will be assigned a 4-digit randomly generated ID number. All scans and blood samples will be labeled with this ID number. Signed consent forms and demographics forms with identifying information will be kept in locked file cabinets stored in a secure location with access limited to Drs. Levy, Ongur, or Bodkin. Computer databases are password protected.

## **SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS**

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Blood samples will be sent to Dr. Raymond Suckow, Analytical Psychopharmacology Laboratory at the Nathan Kline Institute, for amino acid and psychotropic drug levels. Samples will be labeled with a 4-digit randomly generated ID number for each subject, a date and a time of day. The identity of the subjects will not be known to Dr. Sukow.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

N/A

## **RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS**

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A