Northwell Health

RESEARCH PROTOCOL

Protocol Title:	MicroRNAs in neural-derived extracellular vesicles as biomarkers in first episode schizophrenia
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Date Revised:	
IRB Number:	

Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
  - Your study is a registry or repository for data and/or samples, In this case, use *Protocol Template – Registry Studies.* .
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- Start by entering study information into the table above, according to these rules:
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1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

X No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

Schizophrenia is a serious, long-term mental illness that causes significant challenges, including hallucinations, social withdrawal, and difficulty with daily tasks. Currently, doctors primarily diagnose schizophrenia and monitor treatment effectiveness by talking to patients. This process can be slow and imprecise, as we lack quick, reliable tests, like a blood test, to help confirm diagnosis or to tell which treatment will work best for an individual. This gap means patients might experience delays in getting the right care.

This study aims to address this problem by investigating whether tiny molecules called microRNAs (miRNAs), which are found in special "packages" that travel between the brain and the peripheral blood, can serve as helpful indicators for schizophrenia. These brain-derived miRNAs could offer a less invasive way to understand what's happening in the brain.

For this research, we will work with 80 individuals who have recently been diagnosed with schizophrenia and are experiencing their first episode and who are beginning treatment with either aripiprazole or risperidone, along with 80 healthy volunteers. We will collect blood samples from all participants. For individuals with schizophrenia, blood samples will be taken prior to or at the beginning of naturalistic treatment with either aripiprazole or risperidone and then again after 12 weeks of treatment. By comparing the patterns of these brain-derived miRNAs in the blood of patients versus healthy volunteers, and by observing changes in these miRNAs during treatment, we hope to discover if they can help diagnose the illness more quickly and predict how well a treatment will work.

If successful, this study will provide initial evidence that these miRNAs could become valuable new tools for doctors. They could lead to earlier, more accurate

diagnoses of schizophrenia and help physicians choose the most effective treatment for each patient much faster, ultimately improving patient care and outcomes.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

Schizophrenia (SZ) is a significant psychiatric illness characterized by severe symptoms including psychosis, social withdrawal, and cognitive difficulties, leading to impaired daily functioning. Despite ongoing research and understanding, the diagnosis of schizophrenia and the assessment of treatment effectiveness remain heavily reliant on clinical interviews. This method is often subjective, time-consuming (treatment response typically takes weeks to assess), and notably lacks objective, reliable biological indicators (biomarkers) to guide diagnostic and treatment decisions. This absence of clinically relevant biomarkers represents a critical gap in the field, hindering timely and personalized patient care.

Previous research has studied microRNAs (miRNAs) in complex diseases like schizophrenia. Evidence of miRNA dysregulation in schizophrenia has been established through genome-wide association studies, analysis of human post-mortem brain tissue, and various biological fluid studies. Most of these biological fluid investigations have concentrated on miRNAs found in blood, either freely circulating or within peripheral blood mononuclear cells. A more recent and promising approach, already being explored in depression and other neurological disorders, involves measuring miRNAs specifically contained within neural-derived extracellular vesicles (NDEs) isolated from plasma. These NDEs, identified by brain-specific surface markers, are particularly significant because they carry a concentrated cargo of miRNAs that are predominantly found in the brain. Given that these NDEs can be identified and isolated in peripheral blood, the study of these molecules offers a less invasive approach compared to obtaining cerebrospinal fluid or brain tissue.

This current study aims to address the identified knowledge gap by investigating plasma NDE miRNAs as novel diagnostic and treatment response biomarkers specifically in first-episode schizophrenia (FES). Unlike previous studies that might have included individuals with prolonged illness or extensive antipsychotic exposure, our focus on FES participants is a critical differentiator. This choice is deliberate to minimize confounding effects associated with long-term medication use and extended illness duration, allowing for a clearer understanding of the disease's early biological signatures. The importance of the knowledge expected to

result from this study is substantial: successful completion will provide preliminary evidence for the utility of plasma NDE miRNAs as robust biomarkers in schizophrenia. This initial evidence will be crucial for paving the way for their future refinement, comprehensive validation, and eventual clinical implementation, potentially revolutionizing the way schizophrenia is diagnosed and treated by offering objective, brain-specific indicators.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

Aim 1:
Aim 1A. To test NDE miRNAs as diagnostic biomarkers by comparing the plasma NDE miRNA profile from 80 acutely psychotic FES participants at the time of initiating antipsychotic treatment compared to 80 HV to test the hypothesis that a panel of NDE miRNAs will be differentially expressed (DE) in FES participants compared to HV.
Aim 1B. To determine the correlation between baseline NDE miRNAs, psychopathology ratings, and neurocognitive tests.

Aim 2:
Aim 2A. To test NDE miRNAs as treatment response biomarkers by testing if baseline NDE miRNA levels predict response to open label treatment with risperidone or aripiprazole in a 12-week-long mechanistic clinical trial.
Aim 2B. To determine the correlation between longitudinal changes in NDE miRNA levels in relationship to symptom improvement and changes in neuropsychological tests.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
    - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

Our institution, the Zucker Hillside Hospital (ZHH), has been at the forefront of designing and conducting studies in FES for the past four decades, as demonstrated by several publications (Gallego et al., 2011; Kane et al., 1982; Kane et al., 2016; Lieberman et al., 1992; Robinson et al., 2006; Robinson et al., 2015a; Robinson et al., 2015b). Importantly, sample sizes for all these studies have been large. In our RCT comparing aripiprazole and risperidone in FES (Robinson et al., 2015b), 198 FES individuals were recruited, and in our last neuroimaging prospective study

(Clinical Trials.gov ID: NCT02822092; PI: A Malhotra), 150 FES participants were enrolled and completed a baseline MRI. Therefore, we are confident that we will be able to recruit the sample size proposed in this application (80 FES and 80 HV) over 5 years. In addition, the titration schedule for aripiprazole and risperidone that will be used in this study was initially developed for a double-blind RCT conducted at ZHH (Robinson et al., 2015b) and has been also used in our last mechanistic neuroimaging clinic trials with FES participants (R01MH108654, R01MH134883) (Cao et al., 2023). Moreover, this titration schedule for these two medications is not only used in our clinical trials but also has been adopted by our clinicians in inpatient units and at the Early Treatment Program, a specialty clinic for FES individuals. In this treatment schedule, the dose of risperidone or aripiprazole is very slowly increased, as FES individuals are more sensitive to side effects. Using this approach, we found that FES individuals respond to half the dose of typical dose of antipsychotic medications used with multi-episode chronic patients (Gallego et al., 2011). Therefore, the usual mean modal dose used in our studies is approximately 3 mg/daily for risperidone and 15 mg/daily for aripiprazole. Thus, we are confident that we will be able not only to recruit enough FES participants but also to treat these individuals appropriately while minimizing side effects.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

FES participants will be recruited from the Adult Behavioral Health crisis center and the inpatient and outpatient services at the ZHH, as well as from the emergency room at the Long Island Jewish Medical Center, a large general hospital affiliated with Northwell Health located adjacent to the ZHH and which provides acute emergency care 24/7. Healthy volunteers (HV) will be recruited using the posting of IRB-approved advertisements in the community, in printed and electronic media (the Northwell Health website, through Healthport, E-News, and Craigslist), and through word of mouth.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or*

others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol

- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Inclusion criteria. We will recruit patients with an acute first episode of psychosis with DSM-5 diagnosis of schizophrenia, schizoaffective, schizophreniform disorder, or psychosis Not Otherwise Specified (NOS). In addition, we will require: (1) current positive symptoms rated ≥4 (moderate) on one or more of these BPRS items: hallucinatory behavior, unusual thought content, grandiosity, conceptual disorganization; (2) early phase of illness as defined by having taken antipsychotic drugs for a cumulative lifetime period ≤2 weeks; (3) age 15 to 40; (4) receiving or about to start naturalistic treatment with either aripiprazole or risperidone; and (5) competent to sign informed consent.
Exclusion Criteria. These include: (1) serious neurological or endocrine disorder; (2) significant risk of suicidal or homicidal behavior; (3) cognitive limitations due to a previous diagnosis of intellectual disability or any factor that would preclude informed consent; (4) a DSM-V diagnosis of major depressive disorder with psychotic features, bipolar disorder, manic or depressed with psychotic features or substance-induced psychotic disorder; (5) meeting SCID-5 substance use disorder, moderate or severe for any substance (other than nicotine) within 3 months of study entry or SCID-5 substance use disorder, mild for any substance other than nicotine, cannabis, or alcohol; (6) pregnancy.

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

80 First Episode Schizophrenia and 80 Healthy Volunteers individuals will be recruited over 5 years.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

Individuals will participate in the study for a duration of 12 weeks. They will have a baseline visit on day 0, a visit every week for the first 4 weeks and then visits every 2 weeks until week 12.

All subjects are expected to be enrolled by the end of 5 years. The study is expected to be completed 5 years after the start date.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

Primary Endpoint(s)

- The diagnostic performance (e.g., sensitivity, specificity, Area Under the Curve [AUC]) of a panel of plasma NDE miRNAs in differentiating acutely psychotic First-Episode Schizophrenia (FES) participants from Healthy Volunteers (HV).
- The predictive performance of baseline plasma NDE miRNA levels for clinical response to antipsychotic treatment (aripiprazole or risperidone) in FES participants.

Secondary Endpoint(s)

- The correlation between baseline plasma NDE miRNA levels and baseline psychopathology ratings and neurocognitive test performance in FES participants.
- The correlation between longitudinal changes (baseline to 12 weeks) in plasma NDE miRNA levels and changes in psychopathology ratings and neurocognitive test performance in FES participants.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

Consenting patients will have a complete baseline psychiatric evaluation; physical exam and laboratory testing will be used to evaluate medical exclusion criteria. A full baseline clinical and cognitive battery will be performed as described under "Clinical Assessments" below.

Pregnancy Testing: This study does not involve administration of experimental medications or interventions by the research team. Antipsychotic medications are prescribed and managed by participants' treating psychiatrists as part of standard clinical care. Therefore, pregnancy testing is not performed by the research team as a study procedure. For participants recruited from the inpatient and outpatient units, pregnancy test results obtained as part of routine clinical care will be reviewed on the Electronic Medical Record and documented by the research team prior to enrollment. If a participant is found to be pregnant or becomes pregnant during the course of the study, they will be withdrawn from the study.

Urine toxicology: Urine toxicology testing will be performed at baseline (week 0) as part of the medical evaluation to rule out medical conditions associated with psychosis and to assess for substance use. Results will be shared with the participant's treating clinicians. A positive urine toxicology result will not automatically exclude a participant from the study. However, participants who meet SCID-5 criteria for moderate or severe substance use disorder for any substance (other than nicotine) within 3 months of study entry, or SCID-5 criteria for mild substance use disorder for any substance other than nicotine, cannabis, or alcohol, will be excluded. All toxicology results will be included in a research progress note in the participant's electronic medical record (EMR).

Clinical Assessments. Clinical assessments will be conducted at study baseline and weekly for the first month and then every other week until week 12. Psychopathology ratings will be conducted by raters with ample experience assessing FES participants and who conducted ratings in our prior studies. At baseline (week 0), a medical evaluation, including EKG and urine toxicology, will be conducted to rule out any medical condition associated with psychosis. A clinical interview is then conducted to arrive at a clinical diagnosis using the Structured Clinical Interview for Axis I Disorders (SCID-5-RV). Psychopathology will be assessed at all study visits using the Brief Psychiatric Rating Scale – Anchored version (BPRS-A), the Schedule for Assessment of Negative Symptoms (SANS) the Clinical Global Impressions Scale (CGI), and the Columbia Suicide Severity Rating Scale (CSSRS). In addition, we will collect the NIMH common data elements: PHQ-9 and GAD-7 and WHODAS 2.0. In the event that a participant endorses suicidal ideation on the C-SSRS, PHQ-9 (item 9), or SCID-5, the research staff will immediately notify the Principal Investigator, Dr. Juan Gallego, as well as the treating psychiatrist. If participants are still hospitalized, we will inform the inpatient treating psychiatrist who will determine if patient requires 1:1 observation or any other intervention. If participants are no longer hospitalized, we will both notify the outpatient treating psychiatrist and place the patient on 1:1 observation while Dr. Gallego evaluates the patient. Dr. Gallego will conduct a

comprehensive suicide risk assessment. If the participant is considered the be of low-risk, Dr. Gallego will document findings, notify the participant's treating psychiatrist (with appropriate consent), provide crisis resources (988 Suicide and Crisis Lifeline), and arrange safety planning and follow-up. If Dr. Gallego considers that patient is a risk to self or others, he will arrange for immediate admission to ZHH following the ZHH internal procedures for admission of patients receiving treatment at the ambulatory outpatient department. If Dr. Gallego is not available, the research staff member will be instructed to call for support from the ZHH Ambulatory Outpatient Department, as specified in the AOPD ZHH internal guidelines, and escort the patient to either the Zucker Hillside Hospital Crisis Evaluation Clinic or the LIJ emergency department. All research staff members conducting clinical research assessments with patients will be trained and informed about the specific ZHH AOPD procedure to obtain help from ZHH AOPD and EMS in case of acutely suicidal patients.

Vital signs (including weight and waist circumference) will be obtained at all study visits. To assess for extrapyramidal symptoms, we will administer the Simpson-Angus scale for Parkinsonism and the Barnes Akathisia Scale. The Simpson Dyskinesia Scale will be administered at week 0 to assess for any baseline dyskinetic movements and at week 12 for any emerging symptoms of tardive dyskinesia. At every study visit, we will administer the Systematic Assessment for Treatment Emergent Events (Specific Inquiry (SAFTEE-SI) for any emerging side effects. A metabolic panel is typically obtained at the time of admission to the hospital, so it is not being included in this proposal, but results will be evaluated by the research psychiatrist prior to initiating an antipsychotic medication.

Antipsychotic levels will be obtained monthly to help address non-adherence to research psychiatrists and will be explored as a covariate in statistical analysis.

Cognitive testing: The MATRICS Consensus Cognitive Battery, the FDA-approved standard in the field for examination of cognitive effects in clinical trials for patients experiencing psychosis, will be administered at baseline and at 12 weeks. If a participant wishes to leave before week 12, we will offer an exit visit similar to week 12, which includes a neurocognitive assessment.

Medication. Participants entering the study will be either about to start treatment or already receiving treatment with aripiprazole or risperidone, as prescribed by their treating psychiatrist and based on their own preference and clinical judgement. The treating psychiatrist will discuss with potential research participants the risks and benefits of antipsychotic treatment, as part of their routine clinical treatment procedures. Only those patients who already agree to be on aripiprazole or risperidone treatment or who already started antipsychotic treatment, as provided by their treating psychiatrist, will be eligible to participate in the study. The research team will not dictate the choice of antipsychotic or the dose being provided. Aripiprazole and risperidone are both FDA-approved and first-line antipsychotic medications for the treatment of schizophrenia and are the most commonly used antipsychotic medications for FES individuals in our institution. Treating psychiatrists at our institution have been educated to follow the suggested titration schedule for the clinical treatment of all FES individuals. Treating psychiatrists will be allowed to use benztropine mesylate for parkinsonism or acute

dystonic reactions, propranolol or lorazepam for akathisia, lorazepam for agitation, and ramelteon or trazodone for insomnia, if needed.

Table 1.

Timepoint (End of Week N)	0	1	2	3	4	6	8	10	12
Informed consent	X								
Med Eval, EKG, Utox, SCID-5-RV	X								
BPRS/SANS/CGI/CSSRS	X	X	X	X	X	X	X	X	X
Vitals/weight	X	X	X	X	X	X	X	X	X
SAFTEE-SI	X	X	X	X	X	X	X	X	X
SAS, BAS	X	X	X	X	X	X	X	X	X
Simpson-Dyskinesia Scale	X								X
PHQ-9, GAD-7, WHODAS 2.0	X	X	X	X	X	X	X	X	X
Antipsychotic levels					X		X		X
MATRICS Cog Battery	X								X
Blood collection for NDE microRNA analysis	X								X
Genetic Testing	X								

Rater training and rater reliability. The ZHH has >20 years of experience conducting clinical trials with FE participants. Raters at our institution undergo rigorous training to be initially certified and then maintain interrater reliability for all assessments. Intraclass correlation coefficients from our previous first episode psychosis study with three psychopathology raters for the items comprising the Thought Disturbance factor range from 0.79-0.90.

Blood collection: Two K2EDTA 10-ml blood tubes will be collected at baseline (week 0): one will be used for miRNA analysis and the second tube will be used for genetic analysis. At week 12, a single 10 mL K2EDTA blood tube will be collected to perform follow-up miRNA analysis. If a participant wishes to leave before week 12, we will offer an exit visit similar to week 12, which includes a blood draw using a single 10-ml K2EDTA tube for miRNA analysis.

Sample processing. Blood will be collected in 10 mL K2EDTA (lavender top) tubes. Tubes will be centrifuged at 200 g for 15 minutes at 4°C to separate plasma from red blood cells. The plasma (avoiding the buffy coat layer) will be transferred into 1.5 mL cryovials. These cryovials will then be centrifuged at 4,500 g for 10 minutes at 4°C to pellet platelets. The platelet-free plasma will be carefully transferred to new cryovials without disturbing the platelet pellet at the bottom, then flash-frozen with liquid nitrogen and stored at -80°C. Frozen plasma samples will be shipped every 2 months to the University of Alabama at Birmingham laboratory of Dr. Yogesh Dwivedi for neuron-derived extracellular vesicle (NDE) miRNA analysis. Samples will be shipped with only an ID code and date of collection; no protected health information (PHI) will be included. Following analysis, data will be returned to Northwell Health for statistical analysis.

Plasma NDE and RNA isolation: Exosomes will be isolated by centrifuging plasma followed by dilution of the supernatant with PBS and centrifugation at 20,000g x 20 min. The supernatant will be spun down at 200,000g x 2h at 40C. The pellet will be suspended in PBS and immunoprecipitated using L1/NCAM antibody coupled covalently to magnetic beads. RNA will be isolated from an Invitrogen™ RNA isolation kit that extracts highly pure total RNA, including a small RNA fraction from exosome. Synthetic "Spike-in" controls and RNAse inhibitors will be added at the time of RNA isolation. The quality of RNA will be checked; only those will be included that show no sign of degradation (RNA integrity number≥8).
MiRNA sequencing: Construction of libraries and sequencing will be performed at the UAB Heflin Center for Genomic Science. miRNA expression will be analyzed by small RNA sequencing. Low-input RNA from each sample will be used for RNA library preparation. Adapters will be ligated to total RNA, multiplex primers will be hybridized, and reverse transcription (RT) will be accomplished using SuperScript III RT (Life Technologies).
Bar codes with uniquely indexed primers will be attached to each cDNA library and amplified. Size-selected libraries will then be quantified using the qPCR-based Library quantification kit with some modifications for low-input RNA (Kapa Biosystems Inc.). The individually prepared libraries will be used for sequencing using Illumina NovaSeq6000 following 20 million 50-bp single-end reads. NDE isolation and miRNA sequencing will be conducted by a staff member at Dr. Dwivedi's laboratory who will be blind to participant's group identity (FES vs. HV), to decrease risk of bias during analyses.
Genetic Analysis Procedures
Sample Collection: A single blood draw for genetic analysis will be conducted at baseline (week 0). Approximately 10 mL of blood will be collected in a K2EDTA vacutainer tube specifically for genetic analysis. This is in addition to the blood collected for miRNA analysis.
Scope of Genetic Testing: Whole genome sequencing will be performed on DNA extracted from blood samples. This broad sequencing approach allows for comprehensive analysis of genetic variation across the entire genome that may be associated with psychosis, treatment response, or related clinical outcomes.
Sample Processing and Storage: Blood samples will be processed to extract DNA. DNA samples will be assigned a unique study identification code and stored in a secure, locked freezer at -80°C in the Principal Investigator's laboratory. All identifying information will be removed from samples prior to genetic analysis. Samples will be stored indefinitely to allow for future re-analysis as new scientific questions and analytical methods emerge.
Genetic Data Storage: Genetic data will be stored on secure, password-protected servers maintained by Northwell Health. Access will be restricted to authorized study personnel. Genetic data will be stored indefinitely. Nearly all substantial progress in complex genetics research has been enabled by an ethic of data sharing within the research community. Across biomedical disciplines, the accumulation of increasingly large datasets required for genetic discovery has been made possible by the persistent storage of genetic data over time. Long-term storage

allows for re-analysis as new analytical methods are developed and enables researchers to address new scientific questions that emerge over time.
Data Sharing: Since the genetic sequencing is not directly supported by NIH funds, we are not required to deposit genetic data in dbGaP or other NIH repositories. However, we may share de-identified genetic data with qualified researchers in the future to advance scientific knowledge. Any data sharing will be conducted in accordance with participants' consent preferences and will be subject to strict data use agreements that limit access to qualified researchers for approved scientific purposes only. We will use the NIH consent template for genomic data sharing to provide participants with clear options regarding future data sharing.
Return of Results: No return of individual genetic results or incidental findings is planned.
Withdrawal of Consent: Participants will be informed that they can withdraw consent for future research use of their samples at any time. If a participant withdraws consent, they will be informed that all previously submitted de-identified samples shipped for analysis outside Northwell cannot be retrieved. On the other hand, all samples stored locally at Northwell will be destroyed if participants would like to avoid those samples from being used.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

Sample Size and Attrition Considerations:

For Aim 1: The proposed sample size is 160 (80 FES participants and 80 healthy volunteers) and reflects the number of enrolled participants needed for the cross-sectional comparison of miRNA profiles between groups. This analysis requires baseline data only, so attrition is not a concern for Aim 1.

Accounting for Attrition in Power Analysis:
In our prior FE studies conducted at our institution, attrition rates were 15% *(Robinson et al., 2019)*. The power analysis for Aim 2 demonstrates that with a total sample size of 80 participants, the lower limit of a 95% confidence interval for AUC with Binary Elastic Net Regression (BENR) will be 0.69 if the estimated AUC value is 0.80. Based on a simulation study by Kirpich et al., with a sample size of 50 and 2050 features, Elastic-Net regressions with certain specific choices of the α-parameter have > 80% power to select features with Cohen's d value (effect size) ≥ 0.8. Therefore, our larger proposed sample size provides sufficient power to detect features with large effect sizes and serves as a buffer for any potential loss of data related to attrition.

Aim 1A. Analysis of differentially expressed miRNAs:

Data will be cleansed to remove outliers and then normalized using spike-in RNAs. After the removal of adapters and low-quality tags using Fastq Mcf and PRINSEQ, the miRNA-seq data will be mapped to the human genome UCSC hg19 by bowtie to analyze expression and distribution in the genome. The sequences will be aligned to Genbank and Rfam- version 11 databases to screen and remove rRNA, scRNA, snoRNA, snRNA, tRNA associated tags and to align with noncoding sRNAs. Then, the small RNA reads will be annotated to miRBase database using bowtie to identify known miRNA expressions. Reads will be normalized with reads per million. The reads for each miRNA will be calculated for Log2 ratio and median-centered values. Clustering will be performed by the average linkage method using Pearson correlation. Differential miRNA expressions and statistical analysis will be done in the R/Bioconductor using the DESeq package. The Z-test will be applied to show statistical significance in the differential expression (Cui et al., 2003). The Benjamini and Hochberg method will be applied to correct the p values assigned by the Z-test (Benjamini et al., 1999). miRNAs showing significant changes will be further analyzed.

In order to account for potential collinearity logistic regression with Elastic Net penalty for feature selection will be used as a secondary analytic strategy. The dependent variable will be a binary indicator variable for FES participants versus HV, and the independent features will be the variables from a panel of NDE miRNAs. Compared to few other choices of machine learning models, Binary Elastic Net Regression (BENR) was chosen because it generates intuitive and interpretable models. Elastic Net penalty exhibits more efficient and stable performance compared to other shrinkage and selection methods such as Lasso. In addition, Elastic Net regularization encourages grouping effect, where strongly correlated features tend to be in or out of the model together (Zou et al., 2005). Thus, this method is suitable for high-dimensional datasets with smaller sample sizes especially in the presence of correlations among covariates. As sensitivity analysis, in order to assess the predictive capabilities of the features selected, other machine learning models suitable for the proposed sample size such as random forests, gradient boosting regression trees and support vector machines (SVM) will also be employed. Machine learning models will especially be employed to assess whether predictive performance with only differentially expressed features detected via BENR is over and above the performance based on the full panel of miRNAs. We will begin with highly interpretable and person specific machine models such as random forests and progressively employ more robust ensemble methods such as gradient boosting regression trees which trains and combines several weak regression trees to make accurate predictions. SVM models that incorporate nonlinear relationships between the features and the binary dependent variable will also be employed to assess the predictive capabilities. Random shuffle cross-validation (CV) with 25 iterations will be used for all machine learning models and performance measures such as AUC, accuracy, sensitivity and specificity will be averaged across the CV iterations and reported. Linear regression models as well as the above-mentioned machine learning models will be utilized to assess the impact

of differentially expressed miRNAs on neurocognitive and psychiatric symptoms **(Aim 1B).**

Power Analysis. It was conducted using the shiny-app/web-interface for the R package entitled 'RNASeqSampleSize' (Li et al., 2013; Zhao et al., 2018), available as part of the Bioconductor project. In RNASeqSampleSize implementation, minimal average read count and maximal dispersion parameters are used to represent all genes in the RNA sequence experiments, to estimate conservatively sample size or power. The power plot (Figure 5) shows the estimated power to detect various fold-change values (ranging from 1.8 to 2.2) at FDR-level 0.05, with our proposed sample size for Aim-1 (80 completers in each group) assuming 10000 total number of genes included for testing and expected-number of prognostic genes to be 10. Power curves are plotted for various values of 'average read counts and dispersion for prognostic genes.' Note that the total number of genes included for this analysis (10,000) and average read counts of 4 and 5 are conservative choices because the power will be larger for a lower value (e.g. total genes for testing = 5000) for the first parameter and a larger value (e.g. average read count = 500) for the second parameter. Based on the power analysis presented in the plot, our sample size is sufficient to detect a fold-change of 2 or above at ≥80% power at FDR level = 0.05. Assuming a larger dispersion parameter value equal to 1 (and all other parameters the same with average read-count set to 5), foldchange values of 2.6 or above will be detectable with the given sample size at 81% power and FDR level equal to 0.05. Based on our pilot data, we anticipate detecting at least a few (10 or more expected) microRNAs to exhibit a fold-change of 2 or above detectable at 0.05 FDR level. 64 micro-RNAs were detected at 0.05 FDR level in plasma EVs with sample sizes of 20 SZ and 15 healthy volunteers. We anticipate similar results to be seen for the Plasma NDE miRNAs in our proposed study. There were few CSF microRNAs tested in our pilot data with several of them showed fold-change values near 2. With larger sample sizes and much larger number of CSF miRNAs to be tested we anticipate detecting at least 10 or more to have fold-change values ≥ 2 and significant at FDR level = 0.05.

Target prediction and Pathway analysis. The identified miRNA targets will be analyzed using bioinformatics tools: MicroInspector, TargetScan, miRBase, and miRTarBase. MicroInspector spots the correct sites for miRNA interaction in known target mRNAs. This program allows variation of temperature, the setting of energy values as well as the selection of different miRNA databases to identify miRNA-binding sites of different strength. TargetScan predicts biological targets of miRNAs by searching for the presence of conserved 8- and 7-mer sites that match the seed region of each miRNA. The miRBase is a database of published miRNA sequences and annotations. Each entry in the miRBase sequence database represents a predicted hairpin portion of a miRNA transcript with information on the location and sequence of the mature miRNA. miRTarBase is a recently established most extensive collection of more than 3500 manually curated miRNA target interactions from 985 publications, all of which are experimentally validated

by luciferase reporter assay, western blot, qRT-PCR, microarray experiments with overexpression or knockdown of miRNAs, or pulsed stable isotope labeling with amino acids in culture (pSILAC). Targets which are predicted by multiple algorithms, hit by the same miRNA at multiple sites, and hit by multiple different affected miRNAs at sites close to mRNA, will be considered as likely candidates. Since targets are of no use if not expressed in the human brain, we will verify the expression of target genes in the human brain at mRNA levels by analyzing them on Uni-Gene.

To examine the functional output of miRNA/mRNA co-expression at the molecular level, we will use the "topGo" function in R platform to identify the significant enrichment of gene clusters based on their cellular and molecular relationships. GO categories will be separated into molecular functions, biological processes, and cellular components. The two-sided Fisher's test will be used to classify the GO category, and the p-values will be calculated for GO's enriched modules. The p-values of the enriched pathway will be analyzed by DAVID.

Aim 2A. The analytic strategies for Aim 2A and Aim 2B will be Binary Elastic Net Regression (BENR) method. Analytic strategy for BENR will be same as mentioned in Aim-1. The dependent variable for Aim 2A will be the binary treatment response indicator (see next paragraph) and the features included in the model will be baseline NDE miRNA levels. The dependent variables in separate models for **Aim 2B** will be change scores of symptom levels and change scores of neurocognitive measures and the independent variables included in all models will be change scores of miRNA levels. We will conduct our analysis based on change-scores rather than other methods for longitudinal analysis such as linear mixed effects modeling (LMEM) because high dimensional variable selection strategies currently do not exist for methods such as LMEM especially when the scale/dimension of the datasets are very large (>100) like in proposed study. Consistent with our extensive track record in studies of FEP, we will apply a strict criteria for categorical determination of treatment response: all 4 items of the empirically validated Thought Disturbance factor of the BPRS, assessing unusual thought content, severity of hallucinations, grandiosity, and conceptual disorganization, must be below psychotic level (<4), and this criterion must be met for 2 consecutive ratings, with concomitant CGI ratings of much/very much improved.

Power Analysis. With a total sample size of 80 completers, the lower limit of a 95% confidence interval for AUC with BENR will be 0.69 if the estimated AUC value is 0.80. For estimated AUC values of 0.75 and 0.85, the corresponding lower limits will be respectively, 0.64 and 0.75. Based on a simulation study, Kirpich et al. reported that with a sample size of 50 and 2050 features, Elastic-Net regressions with certain specific choices of the α-parameter have > 80% power to select features with Cohen's d value (effect size) ≥ 0.8. Based on Cohen's conventions (Cohen J, 1988), an effect size of 0.8 is considered large. Since we anticipate at least a few features to have large effect sizes, our Elastic-Net regression-based approach will have sufficient power to detect such features. Our target enrollment of approximately 160 participants, accounting for an anticipated 15% attrition rate,

will ensure we achieve the required 80 completers. This larger sample size will also be a buffer for any potential loss of data.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

Blood samples collected as part of this study will be stored long-term (indefinitely) at the Boas Center Biorepository (BCB), located at the Feinstein Institutes for Medical Research, home of the research institutes of Northwell Health to enable future research as new analytical methods are developed. Samples will then be shipped to Dr. Yogesh Dwivedi at the University of Alabama at Birmingham for extracellular vesicle isolation and subsequent RNA extraction and sequencing in batches every two to three months. The BCB maintains ten -80°C, five -20°C and six auto filling liquid Nitrogen freezers, that are externally alarmed and temperature monitored. Freezers are maintained in an airconditioned environment, which is also monitored 24/7 to provide the most optimal freezer operating environment using the Amega monitoring system; all freezers are connected to generator/emergency backup power in case of electrical failures. Freezers have been fitted with efficient space utilizing inventory rack systems to permit easy storage and retrieval of bar-coded specimens. Freezer power requirements are backed up by emergency generator systems. The Amega View freezer monitoring system provides freezer monitoring and datalogging services for all freezers in the Boas Center Biorepository, and the environments in which they are maintained. In the event of a freezer or environment discrepancy/failure, the system is capable of several programmable actions including, automatic voice phone alert system, pager alert system, email notifications, and other application program launch via its connected computer and network. The Amega View system and all temperature log data is stored in the Genetics Data Center and maintained by the informatics group. The BCB utilizes an inhouse developed Laboratory Information Management System (LIMS) to keep track of and manage all biospecimen collections. The BCB LIMS runs on a SQL server backend maintained on internal North well servers and managed by Center for Research Informatics and Innovation. Through BCB LIMS, deidentified biospecimens can be tracked through various workflows, while maintaining proper sample lineage. Unique sample barcodes/ identifiers are generated for each biospecimen entered into the system. The corresponding sample metadata can be customizable depending on each project's needs. LIMS maintains inventory location records for all biospecimens allowing for easy and targeted

retrieval. Sample chain of custody is maintained by keeping records of all distributions and shipments. The system maintains logs of all data updates and changes, inclusive of the user performing the action. The BCB is utilizing this LIMS to maintain biospecimen records for over 50 different research protocols and maintaining inventory records for over one million samples.

Future Research Use: Specimens banked through this protocol may be used for future research related to psychotic disorders, treatment response, neurocognitive function, and related mental health conditions. Participants will be informed through the consent process that their specimens may be used for future research studies that cannot be specified at this time. While all future uses will be for research on mental health and related conditions, participants will not be re-contacted for additional consent for each new analysis unless required by the IRB. Participants may withdraw consent for future research use of their specimens at any time (see "Participant Request for Specimen Destruction" below).

Access to Specimens: Access to specimens at the BCB will be granted only to authorized Northwell Health researchers associated with this protocol. De-identified samples will be shipped to the University of Alabama at Birmingham for miRNA analysis. No other external researchers will have access without additional IRB approval.

Participant Request for Specimen Destruction: Participants may request destruction of their specimens at any time by notifying the Principal Investigator. Specimens not yet shipped for analysis will be destroyed. For specimens already shipped, all identifiers will be destroyed to make the samples anonymous. Anonymous samples cannot be withdrawn from ongoing analyses but will not be used for future research projects.

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
  - *What information will be included in that data or associated with the specimens?*
  - *Where and how data and specimens will be stored?*
  - *How long the data will be stored?*
  - *Who will have access to the data?*
  - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

All information collected will be maintained in accordance with the standards mandated by the IRB. A Certificate of Confidentiality for the study will be automatically obtained from NIH at the time of the notice of award. Any information gained from this research will be kept confidential. Reports from patients' clinical records concerning research observations will not be made available to outside medical facilities without written consent of the patient. Each subject will be assigned a unique identification number and data will be coded

using this number. The coded link to subjects' identities will be kept separate from the database in a locked file cabinet accessible only to the study staff.

All clinical data will be collected on forms, which are identified by a unique participant ID number, protocol ID number, and protocol phase and visit, and are entered into a secured REDCAP (Research Electronic Data CAPture) database. REDCap is a secure, web-based platform, which is used world-wide to collect all types of data ranging from research, to clinical, to operations and has features to support best practices for data confidentiality and security. REDCap data will remain in house and statistical analysis will be carried out by a statistician at Northwell. The biological samples sent to UAB for analysis will only contain the subject's study ID and the date of collection.

All research staff are required to demonstrate their understanding of human subjects' protection issues, including confidentiality issues, by means of passing examinations mandated by the IRB. PHI will need to be collected for subjects to ensure that subjects receive the proper treatment for them (e.g. preventing medication errors) and from all subjects to schedule assessments. The study data files will not have nor need PHI included as the unique identification number will suffice. Information that carries personally identifying material and links to subject identities will be kept in locked files and will be accessible only by the PI and his designees (Santiago Vega - research coordinator). All computer entries will be identified by code only and kept confidential.

Patients' identities will not be revealed in any description or publication of this research. The Northwell Health System, its members and healthcare providers conform to the Health Insurance Portability and Accountability Act (HIPAA). This act includes rules that protect the privacy of health information about subjects that will either be created or used in connection with this research study. We will ask all subjects to grant authorization to use their health information in the informed consent.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

Data Management and Security: Subject information will be stored electronically under the control of the Principal Investigators. Identifiers will be separated from medical information and replaced with linkage codes. Access to Protected Health Information (PHI) will be restricted to authorized Zucker Hillside Hospital investigators. Information linking codes to subjects' PHI will be stored in a locked file cabinet in the locked study coordinator's office, separate from medical data. Access to this linking information will be granted only to study personnel on a need-to-know basis as approved by the Principal Investigator. Data will be stored indefinitely and analyzed by the Zucker Hillside Hospital Department of Psychiatry Research Biostatistics Unit.

Safety Monitor Structure: This study employs a multi-tiered safety monitoring approach:
1. Day-to-Day Safety Monitoring: Dr. Juan Gallego (Principal Investigator) and co-investigator Kelly Garcia will conduct day-to-day safety monitoring. They will review laboratory results at each participant visit and coordinate and share with treating psychiatrists all relevant results from clinical research assessments, including the SAFTEE-SI, which captures emerging adverse effects.
2. Independent Safety Monitor: In addition to the DSMB oversight, Dr. Raphael Braga, a psychiatrist at Zucker Hillside Hospital, will serve as an independent safety monitor for this study. Dr. Braga is independent of the study team and is not a member of the DSMB. Dr. Braga will review all serious adverse events (SAEs) and unanticipated problems involving risks to participants or others (UPIRSOs) within 48 hours of occurrence. He will provide written recommendations regarding continuation of enrollment, protocol modifications, or other safety measures as needed. **3. Data and Safety Monitoring Board (DSMB):** The Zucker Hillside Hospital DSMB will provide semi-annual oversight and review accumulated safety and efficacy data across the study (see Part II below).
Justification for Monitoring Structure: This multi-tiered approach is appropriate given that this is an observational study without experimental interventions administered by the research team. Antipsychotic medication treatment (risperidone or aripiprazole) is prescribed and managed by participants' treating psychiatrists as part of standard clinical care, independent of the research protocol. The research procedures are limited to observational assessments (clinical ratings,

neurocognitive testing, EKG) and blood draws for biomarker analysis, which present minimal to moderate risk. The combination of continuous day-to-day monitoring by the study team, independent review of serious events by Dr. Braga, and periodic comprehensive review by the DSMB provides adequate safety oversight.

Items Monitored: Safety monitoring will include:

- Adverse events (AEs) and serious adverse events (SAEs)
- Unanticipated problems involving risks to participants or others (UPIRSOs)
- Protocol compliance
- Laboratory values
- Medication side effects (via SAFTEE-SI, Barnes Akathisia Rating Scale, Simpson-Angus Scale)
- Suicidal ideation (via C-SSRS)
- Overall clinical status

Frequency of Monitoring: Safety data will be reviewed continuously by the study team at each participant visit (weeks 1, 2, 3, 4, 6, 8, 10, and 12). The Zucker Hillside Data and Safety Monitoring Board (DSMB) will review accumulated safety and efficacy data on a semi-annual basis at minimum, with additional meetings convened as needed for safety concerns.

Rules for Study Interruption or Alteration: This study does not employ traditional stopping rules based on intervention-related adverse event thresholds because it does not involve experimental interventions administered by the research team. Antipsychotic medication treatment (risperidone or aripiprazole) is prescribed and managed by each participant's treating psychiatrists as part of standard clinical care, independent of the research protocol. The research procedures are limited to observational assessments (clinical ratings, neurocognitive testing, EKG) and blood draws for biomarker analysis. Therefore, we will not have stopping rules for our study. However, the study may be temporarily or permanently suspended if:

• Unanticipated serious adverse events related to research procedures (blood draws, clinical assessments, EKG) occur

• The independent safety monitor (Dr. Braga) recommends study modification or suspension based on review of SAEs or UPIRSOs

• The DSMB recommends study modification or termination based on safety concerns identified during semi-annual reviews

• Protocol violations compromise participant safety

Individual participants will be withdrawn from the study if:

• They lose capacity to consent during the study

• They experience a serious adverse event that the treating psychiatrist or PI determines is related to study procedures and makes continued participation inadvisable

• They develop a condition that meets exclusion criteria (e.g., substance use disorder requiring detoxification)

• The participant or their legally authorized representative requests withdrawal

Reporting of Study Suspension: In the event of temporary or permanent study suspension, the following will be notified immediately:

- Northwell Health Institutional Review Board (IRB)
- National Institute of Mental Health (NIMH) as the funding agency
- Zucker Hillside Hospital Data and Safety Monitoring Board (DSMB)
- Independent Safety Monitor (Dr. Raphael Braga)
- All enrolled study participants and their legally authorized representatives (if applicable)

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

The Zucker Hillside Hospital Data and Safety Monitoring Board (DSMB)
DSMB Composition: The DSMB consists of at least five voting members appointed by John M. Kane, M.D., former Chair of the Department of Psychiatry and current Director of the Institute of Behavioral Science at the Feinstein Institute for Medical Research. All voting members are independent of the Zucker Hillside Hospital and have no conflict of interest with the research teams conducting the trials. Membership includes:

- Biostatisticians
- Clinicians with clinical trial experience
- Experts in the patient populations being studied
- Consumer advocates

Dr. John Kane serves as an ex officio member without voting privileges, as does a physician investigator liaison from the Zucker Hillside Hospital Psychiatry Research Division. All full voting Board members are not Zucker Hillside Hospital employees and have no direct involvement with the clinical trials under review.
Independence Confirmation: All DSMB voting members are independent of the study investigators, have no financial conflicts of interest related to the study interventions, and are not employees of Northwell Health/Zucker Hillside Hospital.
DSMB Responsibilities: The DSMB will:
A) Monitor adverse event reports to determine whether their nature, frequency, and severity are consistent with expectations. In case of unexpected events, the DSMB may introduce new monitoring tests, alter inclusion/exclusion criteria, or recommend modifications to consent documents.
B) Review and approve or disapprove modifications to study protocols and consent documents to ensure adequate protection of human subjects in terms of benefits and risks.
C) Periodically review accumulated data (semi-annually at minimum) to monitor patient safety, evidence of adverse treatment effects, and substantive protocol

modifications proposed by investigators that affect the risk/benefit evaluation prior to implementation.

Relationship Between DSMB and Day-to-Day Safety Monitoring: The DSMB provides semi-annual oversight and reviews accumulated safety data across the entire study to identify trends and patterns that may not be apparent from individual case reviews. This periodic comprehensive review complements the continuous day-to-day safety monitoring conducted by the study investigators (Dr. Gallego and Kelly Garcia) at each participant visit and the independent review of individual serious adverse events by Dr. Raquel Braga. Study investigators will report all SAEs and UPIRSOs to the DSMB at semi-annual meetings and will convene emergency DSMB meetings if safety concerns warrant immediate review.

Meeting Schedule: The DSMB meets semi-annually via teleconference, mail, or email communication as determined by Dr. Kane and the DSMB Chair. Unscheduled meetings may be convened if data warrant immediate attention.

Meeting Format and Voting: Meetings may include closed sessions, with appropriate trial representatives (PI, coordinators, co-investigators) available for consultation. A majority of voting members (three) constitutes a quorum. Each full Board member has one vote per issue. If no decision is reached, the Chair resolves the issue. Members may document minority opinions in the meeting minutes.

Reporting: The DSMB Coordinator drafts minutes for review by the DSMB Chair and Dr. Kane within one month of each meeting. Minutes include DSMB conclusions regarding continuation or termination of trials under review. If study termination is recommended, explicit reasons are stated. DSMB decisions are provided to study investigators and relevant reports are filed with regulatory agencies as required.

Data Reporting to DSMB: Reports submitted to the DSMB include:

- Adverse events (with Serious Adverse Events reported within 48 hours)
- Safety and efficacy data (as needed to evaluate adverse events)
- Sample size and missing/incomplete data
- Proposed study modifications (submitted 3 weeks before scheduled meetings)
- Annual IND reports (if applicable)

Data from blinded studies are presented without treatment codes unless the DSMB requests unblinding for meaningful interpretation.

Confidentiality and Conflict of Interest: All DSMB members sign confidentiality assurances before participation. Members complete Disclosure Forms prior to each meeting outlining financial interests in study drugs and professional relationships with sponsors or investigators. Members with conflicts of interest recuse themselves from relevant discussions and votes. If fewer than three conflict-free members are available, ad hoc members are invited to ensure adequate monitoring.

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs. The Investigator or the Sponsor (if applicable) may also discontinue subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.
If the Investigator becomes aware of any serious, related adverse events after the subject completes, withdraws or is discontinued from the study, they will be recorded in the source documents and on the CRF. Refer to previous subsection for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

For participants unable to tolerate one of the two antipsychotic medications, the treating psychiatrist will give them the option of switching to the other antipsychotic medication being offered in the study. If the treating psychiatrist decides that the participant requires an antipsychotic medication other than aripiprazole or risperidone due to poor tolerability, poor response or any other reason, they will be withdrawn from the study and will continue naturalistic treatment in the inpatient unit, if hospitalized, or with another outpatient psychiatrist in the Early Treatment Program at the Zucker Hillside Hospital.

If a participant wishes to leave before week 12, we will offer this participant to conduct an exit visit similar to week 12, which includes a blood draw to obtain blood for NDE miRNA analysis and a neurocognitive assessment

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to results*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

The main risks to participants are: 1) risks of blood collection, 4) risks of loss of confidentiality, 3) risk of genetic analysis, 4) risks of other study procedures.

These are presented below followed by a discussion on procedures to minimize risks.

1. Risks of blood collection: The screening blood draw could cause momentary pain from insertion of the needle and, occasionally, a small bruise at the site of the draw or infection. This bruise will heal within several days. Two separate blood draws will be performed at baseline (week 0) and one at week 12: one for miRNA analysis (10 mL) and one for genetic analysis (10 mL at baseline only).
2. Risks of loss of confidentiality: Subjects are told about the possibility information may become known to unauthorized individuals.
3. Risk of genetic analysis:
There is a potential risk of loss of confidentiality related to genetics data. Genetic information could theoretically be misused in ways that affect participants' insurance eligibility, employment opportunities, or personal privacy if inappropriately disclosed.
Specific genetic risks include:
a) Privacy and Confidentiality: Although genetic samples and data will be de-identified, there is a small risk that genetic information could be re-identified through advanced techniques or if combined with other publicly available information. This could potentially reveal sensitive information about the participant or their biological relatives.
b) Familial Implications: Because genetic information is shared among biological relatives, findings from genetic analysis could potentially have implications for participants' family members, even though no individual results will be returned.
c) Psychological Impact: Some participants may experience anxiety or distress about having their genetic information analyzed, even though individual results will not be returned.
d) Data Sharing Risks: The study involves potential future sharing of de-identified genetic data with qualified researchers in the research community. While such sharing is subject to strict data use agreements and privacy protections, there is a theoretical risk that genetic data could be misused if these protections fail.
e) Indefinite Storage: Genetic samples and data will be stored indefinitely to enable future research. Long-term storage increases the theoretical risk of future privacy breaches, though safeguards are in place to minimize this risk.
f) Unknown Future Uses: Participants' genetic samples and data may be used for future research studies that cannot be specified at this time. While all future uses will be for research on mental health and related conditions, participants will not be re-contacted for additional consent for each new analysis unless required by the IRB.
4. Risks of other study procedures: The clinical interview may involve revealing sensitive or personal information. Therefore, there is the possibility that subjects will become annoyed or upset with the assessment questions. The urine toxicology screen may reveal the usage of illicit substances.**Protection against risks:**
Blood collection: A trained phlebotomist will conduct blood draws, and appropriate bandaging will be applied to minimize pain and the risk of hematoma. Aseptic technique is routinely used to reduce the risk of infection.

Loss of Confidentiality: All information collected will be maintained in accordance with the standards mandated by the IRB. Furthermore, a Certificate of Confidentiality is automatically given by the NIH at the time of the notice of award. Any information gained from this research will be kept confidential. Reports from patients' clinical records concerning research observations will not be made available to outside medical facilities without written consent of the patient. Each subject will be assigned a unique identification number and data will be coded using this number. The coded link to subjects' identities will be kept separate from the database in a locked file cabinet accessible only to the study staff. All research staff are required to demonstrate their understanding of human subjects' protection issues, including confidentiality issues, by means of passing examinations mandated by the IRB. PHI will need to be collected for subjects to ensure that subjects receive the proper treatment for them (e.g. preventing medication errors) and from all subjects to schedule assessments. The study data files will not have nor need PHI included as the unique identification number will suffice. Information that carries personally identifying material and links to subject identities will be kept in locked files and will be accessible only by the PI and his designees (e.g., research coordinator). All computer entries will be identified by code only and kept confidential. Patients' identities will not be revealed in any description or publication of this research. The Northwell Health System, its members and healthcare providers conform to the Health Insurance Portability and Accountability Act (HIPAA). This act includes rules that protect the privacy of health information about subjects that will either be created or used in connection with this research study. We will ask all subjects to grant authorization to use their health information in the informed consent.

Adverse Events: All types of adverse events, including serious, not serious, unanticipated problems involving risks to subjects or others (UPIRSOs) will be collected every study visit of the mechanistic clinical trial using the Systematic Assessment for Treatment Emergent Events (Specific Inquiry (SAFTEE-SI) for any emerging side effects. The IRB for Northwell Health requires immediate notification (within 7 calendar days of PI awareness) of adverse effects that fulfill the following three criteria: 1) they are unexpected; 2) they are related or possible related to the study, and; 3) the harm suggests that the research study places subjects at greater risk of harm that was previously known or recognized. Those adverse events that do not fulfill the three criteria must be submitted at the time of the IRB progress report. In addition, and as per NIMH Reportable Events Policy, any unexpected serious adverse events or any UIRSOs will be notified to NIH within 10 business days of the investigator learning about the event. Other adverse events or serious adverse events that are either expected or unrelated to the study will be notified to NIH as part of the annual progress report.

Genetic Analysis: Several safeguards are in place to protect participants and minimize these risks. All samples will be stripped of personal identifiers according to standard practice before genetic analysis. Genetic samples will be stored in locked freezers at -80°C with restricted access, and genetic data will be stored on secure, password-protected servers maintained by Northwell Health. If a participant notifies the study team of their desire to withdraw after sample collection, the study

team will immediately destroy all identifiers linking the participant to their sample, making it anonymous. Anonymous samples cannot be withdrawn from ongoing analyses but will not be used for any new future research projects. Participants may also request that their sample be destroyed rather than anonymized. Participants will be fully informed through the consent process that DNA data will not be returned to them, which protects them from possible misuses of genetic information as it relates to insurance, employment, or other personal matters. This practice also protects participants from legal uncertainties, as the laboratories involved are not approved for distribution of clinical data. All data shared through repositories or with other qualified researchers in the future will be de-identified and subject to strict data use agreements that limit access to qualified researchers for approved scientific purposes only. Federal protections under the Genetic Information Nondiscrimination Act (GINA) also prohibit health insurers and employers from discriminating based on genetic information. The Certificate of Confidentiality provided by NIH also protects against compelled disclosure of identifying research information. Genetic data will be stored indefinitely because nearly all substantial progress in complex genetics research has been enabled by persistent data storage within the research community, allowing for re-analysis as new analytical methods are developed and enabling researchers to address new scientific questions that emerge over time.

Other study procedures: As part of the consent process, subjects will have been informed that they can stop study procedures at any time that they wish. Interviewers will be experienced conducting assessments and will be trained to be sensitive to subject concerns. If a subject becomes distressed, study procedures will be stopped.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

For medical emergencies, participants should call 911 or go to the nearest Emergency Room.
If a participant believes they have been injured as a result of taking part in this research study, they should notify the Principal Investigator as soon as possible. The Principal Investigator's name and phone number are listed on the consent form. Participants will receive medical care and treatment as needed from Northwell Health to treat injuries directly resulting from participation in this study, including injuries related to research-only procedures such as blood collection for miRNA

analysis, genetic analysis, neurocognitive testing, clinical assessments, and electrocardiogram (EKG) However, Northwell Health may bill the participant's insurance company or other third parties, if appropriate, for the costs of care received for the injury. Participants will be instructed to use their own health insurance in the event of research-related injuries. Participants may also be responsible for some of those costs, including deductibles, co-payments, and any costs not covered by their insurance. There are no plans for Northwell Health to provide payment or other compensation for study-related injuries beyond the medical care and treatment provided.

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

There will not be immediate direct benefit to study participants, but the results may be of future benefit to society as a whole and to future patients with psychiatric illnesses, by increasing knowledge about the use of NDE miRNAs as diagnostic and treatment response biomarkers.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

First, we will obtain a partial HIPAA waiver to allow the team to screen and identify via electronic health records potential research participants. In addition, patients will be referred to our study by the patient’s treating psychiatrist in either the inpatient or outpatient services at the Zucker Hillside Hospital. Agreeable potential subjects will be initially screened by the research coordinator, and the PI of this study will join the meeting to continue with the consent process. Subjects will be then explained all study procedures, as well as the potential risks and benefits. Additionally, subjects will be given the opportunity to have family members join and assist in the process. Subjects will be given the opportunity to ask questions. During the process and prior to obtaining consent, the consenting team member will assess the subject's capacity to consent for a research study by applying Paul Appelbaum's framework (Appelbaum,2007), which is routinely used to determine whether patients have capacity to consent for research. This

framework includes assessment of the following four criteria: (1) communicating a choice, (2) understanding the relevant information, (3) appreciating the situation and its consequences, and (4) reasoning about treatment options. The capacity assessment will be documented in the research Electronic Medical Records. Additionally, a quiz (Study Information Review Questionnaire) will be administered at the end of the consent process to ensure the subject's understanding of the study procedures. Patients who are deemed to be incapable of providing consent will not be evaluated further. For those subjects with unclear capacity to provide consent, an outside physician will evaluate the patient. Only those who are considered capable to provide consent by this "outside" physician will be approached for consent.
Loss of capacity during study participation is not expected, as decisional capacity is typically most affected at the very beginning of the illness when psychotic symptoms are most severe. However, if a participant is determined not to have capacity at any point during the study, they will be withdrawn from the study. If capacity improves after a participant has been withdrawn re-consent or further participation will not occur.
Only when subjects are fully informed about the study will they be asked to consent to participate in the study. All subjects will receive a copy of the consent form and will be informed that they can withdraw their consent for participation at any time without consequences to their clinical treatment at the institution.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

We do not foresee any cost that subject will be incurring in by participating in this study. All transportation expenses will be covered and all study procedures will be paid for by the research study.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Subjects will be compensated with $50 for the first and final visit (week 12) and will receive $25 per visit for all other intermediate visits (weeks 1, 2, 3, 4, 6, 8, and 10). The total compensation for completing all 9 study visits is $275. Payment will be provided in cash or via ClinCard at the end of each completed visit.

Payment for Minors: If the participant is a minor (under 18 years of age), payment will be made to the parent or legal guardian at the end of each completed visit.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

Patients will be referred to our study by the patient's treating psychiatrist in either the inpatient or outpatient services at the Zucker Hillside Hospital. Agreeable potential subjects will be initially screened by the research coordinator, and the PI of this study will join the meeting to continue with the consent process. Since the treatment with antipsychotic medications will be provided by the treating psychiatrist outside the research team and there are no greater than minimal risk interventions in our study, we will allow either the PI, co-investigators or the research coordinator to obtain informed consent. Subjects will be explained all study procedures, as well as the potential risks and benefits. Additionally, subjects will be given the opportunity to have family members join and assist in the process. Subjects will be given the opportunity to ask questions.

During the process and prior to obtaining consent, the consenting team member will assess the subject's capacity to consent for a research study by applying Appelbaum's framework, which is routinely used to determine whether patients have capacity to consent for research. This framework includes assessment of the following four criteria: (1) communicating a choice, (2) understanding the relevant information, (3) appreciating the situation and its consequences, and (4) reasoning about treatment options. Importantly, all consenting team members will be trained by the PI to conduct this decision-making capacity assessment. The capacity assessment will be documented in the research Electronic Medical Records. The participant will complete the adult Study Information Review questionnaire to demonstrate understanding of the study procedures. Patients who are deemed to be incapable of providing consent will not be evaluated further. For those subjects with unclear capacity to provide consent, an outside physician will evaluate the patient. Only those who are

considered capable to provide consent by this "outside" physician will be approached for consent.
Only when they are fully informed about the study, they will be asked to consent to participate in the study. All subjects will receive a copy of the consent form and will be informed that they can withdraw their consent for participation at any time without consequences in further clinical treatment in the institution.
Loss of capacity during study participation is uncommon as decisional capacity is typically most affected at the very beginning of the illness when psychotic symptoms are most severe. However, patients will be evaluated at every study visit using clinical research assessments. If there is suspicion from these evaluations, we will conduct a full decision-making assessment and if a participant is determined not to have capacity, they will be withdrawn from the study. If capacity improves after a participant has been withdrawn from the study, we will not re-consent the patient.
Consent will follow IRB approved procedures. Consent will be obtained by primary investigator Dr. Juan Gallego, Kelly Garcia (co-investigator -foreign medical graduate), and Santiago Vega (research coordinator -foreign medical graduate). Consent for patients will occur in the inpatient units or the clinic.

Study Information Review Questionnaire to Assess Understanding:

In order to ensure that subjects understand the fundamental aspects of the study, we require that they demonstrate this by correctly answering a series of specific questions about the study covering key aspects of the study. The Study Information Review Questionnaire is administered as a separate IRB-approved document at the end of the consent discussion to assess participant comprehension before obtaining written informed consent.
The format of the Study Information Review is a question followed by two possible answers. The answers are written in a parallel sentence structure to minimize reading difficulty. We employ the parallel answer format instead of a true/false format because of our experience that subjects with limited education and test-taking skills better comprehend the parallel answer format.
The Study Information Review Questionnaire includes five questions covering:

1. Whether study participation is required to receive treatment
2. Whether participants can withdraw at any time
3. Duration of the study (12 weeks vs 52 weeks)
4. Whether blood tests are involved in the study
5. Whether genetic testing is performed and whether results will be returned to participants

Examples of questions from the Study Information Review are presented below:
DIRECTIONS: Below are questions that people frequently have about the study. Each question is followed by 2 answers. One answer is correct and the other answer is wrong. Please put a check mark next to the correct answer.
Question
1. Do I have to be in the study to get treatment at the hospital?

a) To get treatment, I must be in the study.
OR
b) To get treatment, I do not have to be in the study.

Question 2. If I start in the study, can I leave before it is over?
a) If I decide to be in the study, I must stay until it is over.
OR
b) If I decide to be in the study, I can leave any time that I wish.

Question 3.
How long does the study last?
a) If I want to, I may be in the study for up to 12 weeks.
OR
b) If I want to, I may be in the study for up to 52 weeks.

Subjects must answer correctly all the questions on the Study Information Review before providing informed consent for the study. If a subject answers any question incorrectly, the consenting team member will review the relevant information from the consent form again and re-administer the question until the subject demonstrates understanding. The completed Study Information Review Questionnaire will be maintained in the participant's research file.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

Parental permission will be obtained from one parent or legal guardian during an in-person meeting with the research team. The parent will review and sign an IRB-approved parental permission form after completing a separate IRB-approved Parent Study Information Review questionnaire to demonstrate understanding. The questionnaire mirrors the participant version but substitutes "my child" for "I" where appropriate. All questions must be answered correctly before written permission is obtained. Permission from only one parent is

required as this study involves treatment provided by the treating psychiatrist and does not involve other high-risk interventions.

If the minor is in the custody of a legal guardian or other legally authorized representative, permission may be obtained from that individual after confirming their legal authority with the treating psychiatrist and treatment team. Documentation of legal guardianship will be obtained and placed in the research file.

Written assent will be obtained from all minors (ages 15-17) using an IRB-approved age-appropriate assent form. Prior to signing, the minor will complete a separate IRB-approved Study Information Review questionnaire to demonstrate understanding of key study elements. All questions must be answered correctly before written assent is obtained. The enrollment note will document that correct answers were reviewed and understanding was conveyed for both parent and participant.

Minor participants may turn 18 during the 12-week study period. Participants will be approached before turning 18 to explain the benefits and risks of the study and the need for independent consent. The re-consent process will occur after the participant's 18th birthday. The research team will review the adult consent form and obtain the participant's independent written informed consent to continue participation. The participant will complete the adult Study Information Review to demonstrate understanding. If the participant declines to provide consent, their participation will be discontinued, but data already collected will be retained and used. The participant will be offered continued clinical care outside of the research study.

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*

- *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

N/A

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

N/A

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS X N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *Explain why it is not possible to conduct this research without using the information or biospecimens in an identifiable form*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*

- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

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25. WAIVER OF HIPAA AUTHORIZATION ☐ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*

- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)*

A partial HIPAA waiver will be requested from the IRB to screen inpatient medical records for study eligibility. When an eligible patient is identified through chart review and remains hospitalized, the treating inpatient psychiatrist will be contacted and approval obtained prior to approaching the patient for study participation. In addition to chart screening, recruitment will occur through clinician referrals and patient self-referrals. Patients may self-refer after learning about the study through IRB-approved recruitment flyers or advertisements posted in clinical areas. For clinician-initiated referrals, the referring clinician will obtain the patient's permission before providing their contact information to the research team**.**

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☒ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☐ *poor/uninsured*
- ☒ *Students*
- ☒ *Minorities*
- ☐ *Elderly*
- ☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

Our department has done work on subject selection biases demonstrating the unintended adverse effects on women and minority study participation introduced by restrictive inclusion criteria and other aspects of study design. Based upon these data and the results of other studies, we have carefully considered each aspect of the design to minimize any barriers to study participation. Inclusion criteria are the minimum needed for achieving the study's scientific goals. The projections for enrollment of women and for minorities are based upon the actual subject composition of previous R01 studies on patients with early phase schizophrenia.

The diverse racial and ethnic background of subjects reflects the broad representation of different racial and ethnic groups within metropolitan New York City, the location of the site for the proposed study. The projected representation of women is consistent with the gender distributions found in other studies of early phase schizophrenia (e.g. the national NIMH-funded RAISE ETP project).

Inclusion of Children: Children aged 15 years or older may participate in the study. Most, if not all, of these children will be students. Children under this age are excluded because children with schizophrenia under the age of 15 have specialized treatment needs and thus require separate study.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

N/A

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

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