PROTOCOL TITLE:

The relationship between the efficacy of lumateperone and central glutamate and dopaminergic metabolism: A comparison with risperidone in first episode psychosis

PRINCIPAL INVESTIGATOR:

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Department: Psychiatry Research

VERSION NUMBER: 3

DATE: *05/01/2023*

REGULATORY FRAMEWORK:

Please indicate all that apply (please note that the regulatory framework **does not** mean the funding source):

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☒	FDA (Food and Drug Administration)
☒	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

FUNDING:

Indicate if the protocol is funded. If so, provide sponsor and SPO Huron ERA record number (FPXXXXX)

Intra-Cellular Therapies, Inc, FP00012215

CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No

NIH Definition of a Clinical Trial:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions. An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

Use the following four questions to determine the difference between a clinical study and a clinical trial:

1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
4) Is the effect being evaluated a health-related biomedical or behavioral outcome? ☒ Yes ☐ No

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

For any assistance with registration of your trial or the requirements, please contact HSC-CTSCResearchConcierge@salud.unm.edu

Table of Contents

1. Objectives

1.1. Describe the purpose, specific aims, or objectives.

Aim 1. To examine the differential relationships between antipsychotic efficacy and changes in central dopaminergic and glutamatergic metabolism in lumateperone and risperidone treated early psychosis patients. Brain glutamate and dopamine measures will be collected once in healthy controls to assist in the interpretation of baseline psychosis findings.

Aim 2. To examine the differential relationships between common side effects and peripheral blood metabolic changes in lumateperone and risperidone treated early psychosis patients. Specifically, extra-pyramidal (EPS) effects will correlate with serum prolactin changes and weight-gain will correlate with lipid changes.

Aim 3. (Exploratory, no hypotheses). To examine differences in circular-RNAs in peripheral blood between psychotic patients and healthy volunteers and changes in patients treated with risperidone vs. those treated with lumateperone.

1.2. State the hypotheses to be tested.

Hypothesis 1a). Lumateperone's efficacy will be directly related to both striatal neuromelanin and medial cingulate glutamate changes. **Hypothesis 1b).** With risperidone, the relationship with efficacy will be restricted to striatal neuromelanin changes.

Hypothesis 2a). Risperidone will cause more EPS than lumateperone, and this will be related to greater increases in prolactin. **Hypothesis 2b).** Risperidone will cause greater weight gain than lumateperone, and this will be related to increments in plasma lipids.

2. Background

2.1. Describe the relevant prior experience and gaps in current knowledge.

Lumateperone is an efficacious second generation antipsychotic with dopamine, serotonin, and glutamate effects, a benign safety profile in terms of EPS and metabolic syndrome, and the advantage of a single dose (Correll, et al. JAMA Psych, 2020; Snyder et al, Psychopharm, 2015). Efficacy and safety have been established compared to placebo in chronically-ill psychotic patients (Correll, et al. JAMA psych, 2020). Glutamate abnormalities have been documented in schizophrenia mainly with single-voxel proton magnetic resonance spectroscopy (1H-MRS; Merrit et al, JAMA Psych, 2015). We have recently implemented for the first time whole brain measurement of glutamate (glutamate plus glutamine, i.e.: Glx) with three dimensional echo planar spectroscopic imaging (3D-EPSI) in first episode schizophrenia (Bustillo et al, NPP, 2020). In addition, we have successfully applied magnetic resonance scanning of neuromelanin, a sensitive proxy for dopamine concentration in the

substantia nigra (S-N). The S-N is the origin of the dorsal-striatal terminal fields, where an increased dopamine release has been documented in-vivo in schizophrenia and bipolar-I subjects with positron emission tomography (PET; Cassidy et al, PNAS, 2019). The lumateperone effects on brain dopamine and glutamate have been documented in rodent models of psychosis (Snyder et al, Psychopharm, 2015). In this pilot study, we propose to examine the in-vivo effects of lumateperone on central measures of dopamine and glutamate metabolism and their relationship with efficacy, in early psychosis patients. An early psychosis sample offers a better opportunity to examine brain mechanisms underlying efficacy of novel compounds because of minimization of chronicity and previous treatment effects.

This study will be the first to use 3D ^{1}H-MRS and neuromelanin MRI to examine the clinical significance of the presumed modulation of glutamate and dopamine with the novel agent lumateperone. Though animal studies with lumateperone have documented such effects in models of psychosis, an actual test in humans with psychotic disorders has never been implemented. Finally, though a relationship between DA and glutamatergic dysfunction has long been postulated in psychosis (McCutcheon et al. World Psych 2020), the tools for a direct examination have been limited. Single-voxel 1H-MRS has been the standard to examine glutamate in-vivo. However, a significant limitation of 1H-MRS data in most psychosis studies has been the relatively large voxel sizes needed (several cm3), due to the relatively low signal-to-noise ratio of the measurement, and the practical need, due to time constraints, to examine only one or a few brain regions (Merrit et al, JAMA Psych, 2015). Schizophrenia and bipolar-I (the prototypical psychotic disorders), have broad brain involvement and subtle structural changes (Thompson et al., Trans Psych. 2020), hence a method capable of examining smaller voxel sizes over multiple regions, such as 3D ^{1}H-MRS is advantageous. PET with radioligands, is the standard for measurement of dopamine but it is highly invasive, takes a long time to acquire and is expensive, which limits its implementation in psychotic subjects with no or minimal treatment. S-N neuromelanin MRI is a safe, valid proxy measure of central DA metabolism (Cassidy et al, PNAS, 2019), acquired in a time-frame of minutes, which will be feasible as part of an hour of total MR assessments.

2.2. Describe any relevant preliminary data.

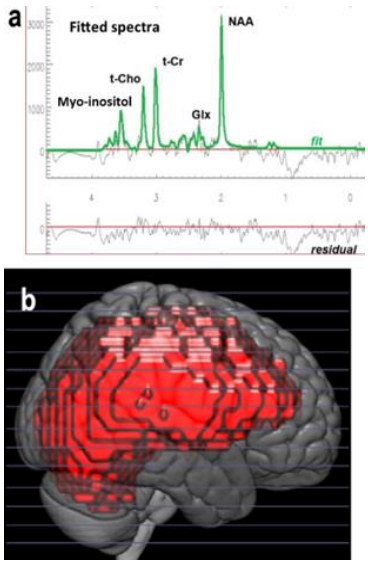

Figure 1

1. Example of EPSI Glx Data. We collected EPSI data in 29 HV in a 3T TIM Trio scanner with a 32 channel head-coil using the following sequence: TE=17.6 ms, TR=1551 ms, TR(H_2O)=511 ms, non-selective lipid inversion nulling with TI=198 ms, FOV=280x280x180 mm, 50x50x18 k-space samples, echo-train length=1000 points, bandwidth=2500 Hz, reduced k-space sampling (acceleration factor=0.7). Processing steps are described in our publication (Bustillo et al, NPP, 2020). Figure 1 illustrates the fitting of a representative spectra in green (a) and the 3-dimensional mask showing coverage in red of Glx with reliable fitting (CRLB≤20) for the whole group (b). Though coverage in the several frontal and basal brain areas is poor, medial cingulate, striatal, thalamic, insular, superior temporal, parietal and occipital coverage is adequate.

2. Example of S-N Neuromelanin Data. We recently collected data in one HV with the new 3T PRISMA scanner at the Mind Research Network (MRN) with a 32-channel head-coil using the following sequence: TR/TE=444/4.11 msec; spatial array of 50 x 50 x 18, FOV 220 mm (corresponding to a nominal voxel size of 0.4 x 0.4 x 1.5 mm^3); flip angle of 40°. To quantify signals in the S-N, we used established methods for preprocessing (Wengler et al. Neuroimage, 2020). Analysis of Functional Neuro-Images (AFNI) software (Cox, *Comput Biomed Res,* 1996) was used to conduct motion correction, average across acquisitions, co-register to the T1 image. We normalized the T1 image to MNI space and applied warping parameters to the co-registered NM-MRI image using the Advanced Normalization Tools, and spatially smooth with 1mm FWHM Gaussian kernel. Regions of interest of the dopaminergic nuclei within the S-N were defined from a high-resolution probabilistic atlas (Pauli et al. *Sci Data.* 2018) (Figure 2). The neuromelanin-MRI contrast ratio (CNR) was calculated as the percent signal difference in neuromelanin-MRI signal intensity at a given voxel in the SN relative to nearby regions that are known to have minimal neuromelanin content (crus cerebri; Knudsen et al, Lancet Neurol, 2018). Voxel-wise CNR values were averaged across high probability voxels.

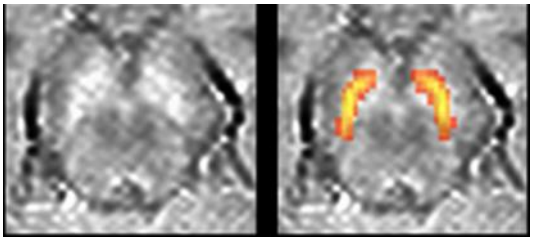

Figure 2

2.3. Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

The pathophysiology of psychotic disorders remains poorly understood and this has prevented the development of novel therapies. The current mainstay of treatment

relies on agents that block DA-2 receptors which are effective for the psychotic symptoms in about 30-60% of patients (Kapur et al, AJP, 2003). However, cognitive and negative symptoms, which account for most of the variance in poor functioning, remain largely untreated. New strategies involving other neurotransmitter systems, including several glutamate-modulating agents (glycine, D-cycloserine, lamotrigine, and polyglumetab) have failed (Marder et al., N Engl J Med. 2019).

There are two significant specific implications for this proposal. First, identifying the location of glutamatergic deficits is critical to inform probe placement for future neuromodulation studies, aimed to improve persistent psychotic symptoms. For example, if a particular cortical area (like the medial cingulate) has persistently increased Glx in partially-responsive patients, low-frequency transcranial magnetic stimulation (TMS) targeting the medial cingulate may result in symptomatic improvement for patients who fail available antipsychotic therapy. Alternatively, clinically-relevant reductions in Glx would support high-frequency TMS targeting specific locations. Second, these studies will also inform anatomical site selection for future postmortem studies of schizophrenia and bipolar-I aimed at examining the molecular underpinnings of these illnesses. This is critical for the development of novel compounds for psychosis that go beyond DA-2 blockade.

3. Study Design

3.1. Describe the study design (e.g., observational; randomized placebo-controlled clinical trial, etc.)

We will examine the relationship between glutamatergic and dopaminergic brain metabolism at baseline in first episode psychosis (FEP) and the impact of standard D2 blockade with risperidone vs that of the new antipsychotic lumateperone. More specifically, we will examine the relationships between glutamate and dopamine central metabolism and efficacy and tolerability in the context of a 6-week randomized controlled trial. Additionally, with a case-control design we will measure neurochemical concentrations in the clinical population (FEP) and contrast them with healthy volunteers (HV). The dependent variables to be assessed are valid metrics of glutamatergic (glutamate, Javitt et al. JAMA Psych 2018) concentrations and dopaminergic metabolism (S-N neuromelanin, Cassidy et al, PNAS, 2019). Our preliminary data supports these can be reliably measured with the MRI Siemens PRISMA scanner locally available at the Mind Research Network (MRN), the local neuroimaging research institute we have been collaborating with for 2 decades.

3.2. Describe blinding, if applicable

Blinding of the drug (lumateperone and risperidone) will be done by the University Hospital Research Pharmacy. Subjects will take only one capsule per day with either 1, 2, 3 or 4 mg of risperidone (titrated blindly based on clinical response) or 42 mg of lumateperone (the single FDA dose approved for antipsychotic effects). Randomization will be done at the University Hospital Research Pharmacy. The subjects, the prescribing research psychiatrist, as well as research staff will be blinded to randomization status.

4. Inclusion and Exclusion Criteria

4.1. Describe how individuals will be screened for eligibility.

Patients with possible psychotic disorder (based in information from referring clinician or loved ones), will be asked about presence of psychotic symptoms (eg: delusions, hallucinations) that persist in the absence of psychomimetic drugs and/or neurological or medical problems likely to cause psychosis. Referrals will be from a clinician who knows the subject or from concerned family members; the DSM-5 diagnosis will be completed by our research team. Clinicians do not have to be members of the study team to refer patients to the study.

4.2. Describe the criteria that define who will be included or excluded in your final study sample, including age. "Age" can be part of a de-identified data set provided ages over 89 are not included. In order to maintain a de-identified classification, all ages over age 89 may be aggregated into a single category of "age 90 or older". If specific ages over 89 are included, then this would be considered a Limited Data Set.

Patient group:

Inclusion: a) Diagnosis of DSM-5 schizophrenia, bipolar-I mania and mixed episodes with psychotic features, schizophreniform, schizoaffective, delusional, and unspecified schizophrenia spectrum and other psychotic disorders, established with SCID-P for DSM-5; b) age between 18 and 40 years old; c) antipsychotic exposure no greater than 50 mg of olanzapine equivalents (Gardner et al. AJP, 2010) in the 7 days previous to baseline assessments.

Exclusion: a) neurological disorder, intellectual disability, history of severe head trauma (unconciousness >10 min); b) diagnosis of active substance use disorder (except for nicotine and cannabinoids [cannabinoids use is a risk factor for psychosis]); c) contraindications to MRI.

Healthy Volunteers (HV) group:

Inclusion: a) age between 18 and 40 years old.

Exclusion: a) current or past psychiatric disorder (assessed with the SCID-NP; subjects with past history of anxiety or depressive disorders receiving no active treatment in the previous 12 months may be included); b) past or current diagnosis of neurological disorder, history of severe head trauma or diagnosis of active substance use disorder (except for nicotine or cannabinoids); c) history of a psychotic disorder in first-degree relatives; d) contraindications to MRI.

4.3. Indicate specifically whether you will include each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent:*
- *Individuals who are not yet adults (infants, children, teenagers)*

- *Pregnant women; Please indicate if pregnant women are included or excluded. Alternatively, state that pregnant women are not being targeted nor is pregnancy being screened for.*
- *Prisoners; Please indicate that prisoners will be excluded. Inclusion of prisoners requires approval from the Office for Human Research Protections (OHRP) and from the NM Corrections Department.*

If subjects with psychotic disorders are unable to consent due to significant disorganization of thinking, the subjects with psychotic disorders may still assent to participation as long as a legally appointed representative (LAR) is willing to consent. Vulnerable populations such as individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners will not be enrolled into the study. During the phone screening process, all potential female participants over the age of 18 are asked if there is any chance that they could be pregnant. The unknown risks of an MRI to a fetus are explained. If they are currently pregnant then they cannot participate. All females whom have menses will have a urine pregnancy test to rule out pregnancy during the screening process before the MRI.

4.4. Indicate if you excluding any particular populations (e.g., women, children, persons not fluent in English, a particular racial or ethnic group, etc.) and provide justification.

Children will be excluded because lumateperone has not been approved for persons younger than age 18. Furthermore, the questions regarding differential relationships between glutamatergic and dopaminergic brain metabolism and efficacy and tolerability of lumateperone versus risperidone, can be fully answered in adults.

4.4.1. If applicable, please state that pregnant women are not being targeting nor will pregnancy be screened for. Provide justification if this is applicable.

During the phone screening process, all potential female participants over the age of 18 are asked if there is any chance that they could be pregnant. The unknown risks of an MRI to a fetus are explained. If they are currently pregnant, then they cannot participate.

4.4.2. If excluding pregnant women, please indicate how investigators will screen for pregnancy.

All females who have menses will have a urine pregnancy test to rule out pregnancy during the screening process before each MRI.

5. Number of Subjects

5.1. If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

N/A

5.2. Indicate the number of subjects to be recruited at this site.

This is a single site study. We plan to recruit up to 35 subjects with psychosis. With a conservative estimate we expect to have 25 such subjects complete the study. We also expect to recruit up to 25 HV and estimate 20 will complete the study.

5.3. Provide sample size justification

This is a pilot study, so there is no preliminary or previous literature available to suggest the strength of the relationship between any changes in glutamate or neuromelanin and changes in psychotic symptoms with any antipsychotic treatment. Hence, no power analysis is presented. However, with the small sample collected, we expect to calculate effect sizes for these relationships to design a well powered future study.

Note 1: When studies involve consent, an individual is considered a research subject once they have provided consent. If the research includes screening procedures after consent, please indicate the number of subjects that need to be recruited and the number that will actually participate in the research post-screening.

Note 2: When studies involve the use of human data or specimens, the number should describe the total number of individuals from whom those data or specimens originated.

Note 3: Over-enrollment (exceeding the numbers described to the IRB) is a protocol violation. If you need to include more subjects, a modification must be submitted to and approved by the IRB prior to doing so.

6. Study Timelines

6.1. Describe:

- *The duration of an individual subject's participation in the research*

The study duration for an individual patient with psychosis will include 12 visits, each about a week apart. Visit 1 will take about 6 hrs. Visit 2, about 3hrs. Visits 3, 5 and 7 about 2 hrs each. Visits 4 and 6 about 1 hr each. Visit 8 about 4 hrs and Visits 9, 10, 11 and 12 about 30 mins each. Hence the expected length of participation will be about 23 hrs over 12 weeks. The study duration for an individual healthy volunteer will include between 4 and 6 hours to be completed in 1 or 2 visits about a week apart.

- *The duration anticipated to enroll all subjects:* 2 years.

- *The expected duration for the investigators to complete the study (complete analysis):* 3 years

7. Study Endpoints

Primary endpoint(s) are typically efficacy measures that address the main research question. Secondary endpoints are generally not sufficient to influence decision-making alone but may support the claim of efficacy by demonstrating additional effects or by supporting a causal mechanism.

7.1. Describe the primary and secondary study endpoints.

Primary endpoint: As per Aim 1, the endpoint is the relationship between **efficacy** (change in positive symptoms score, baseline minus week 6) and changes in anterior cingulate **glutamate** and in the substantia nigra **neuromelanin,** in patients randomized to lumateperone versus risperidone.

Secondary endpoint: Group differences in anterior cingulate **glutamate** and substantia nigra **neuromelanin** between untreated (prior to randomization) psychotic patients and healthy volunteers.

7.2. Describe any primary or secondary safety endpoints.

As per Aim 2, the endpoints are the relationships between changes in extrapyramidal side-effects and in weight, with changes in prolactin and plasma lipids respectively, in patients randomized to lumateperone versus risperidone.

7.3. Describe any exploratory endpoints.

Differences in circ-RNAs between FEP and HVs as well as differences in changes in circ-RNAs between FEP treated with lumateperone and risperidone. Measures of functional connectivity (from rest fMRI); measures of brain volumes (from structural MRI); measures of structural connectivity (from DTI) in psychotic patients vs. HV subjects; also changes in functional connectivity, brain volumes, structural connectivity before and after treatment, and their relationship to change in symptoms, EPS and metabolic measures in psychotic patients. Finally, we will explore the relationships between glutamate and other metabolites (NAA, choline, creatine, inositol) across the brain and neuromelanin, functional connectivity, brain volumes, structural connectivity cross-sectionally (psychosis vs, HV) and longitudinally (in psychosis before and after treatment).

8. Research Setting

8.1. Describe the sites or locations where your research team will conduct the research.

All research activities will be conducted at the Center for Psychiatric Research and the Mind Research Network (Domenici Hall). Due to the ongoing pandemic, we will continue to implement precautions listed by the HSC Research Division. Blood work will be drawn at the University Hospital Tricore labs for FEP and at CPR for HVs.

8.2. Identify where your research team will identify and recruit potential subjects.

The research team will identify potential subjects at UNMH Psychiatric Center (UPC) and the community (through fliers).

8.3. Identify where research procedures will be performed including any laboratory analytics

Clinical and cognitive assessments and neuroimaging analyses will be performed at the Center for Psychiatric Research; image acquisition and some image analyses at the Mind Research Network. Standard of care blood work for patient participants will be drawn and analyzed at the University Hospital Tricore labs. Samples drawn for circular RNAs will be analyzed by Dr. Wylie once he has secured funds.

8.4. Describe the composition and involvement of any community advisory board.

N/A

8.5. For research conducted outside of UNM HSC and its affiliates describe:

N/A

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure/requirements (Note: include any approvals (IRB, facility, or other) with your submission)*

9. Resources Available

9.1. Describe the qualifications of the PI and study staff (e.g., training, experience, oversight) as required to perform the research. When applicable describe their knowledge of the local study sites, culture, and society.

PI: Juan Bustillo has 25 years of experience doing neuroimaging research with this population at UNM Psychiatric Center (UPC) and 17 years in collaboration with the Mind Research network (MRN). He has over 150 peer reviewed publications and multiple intra and extramural funding awards. Dr. Rhoshel Lenroot is a Professor of Psychiatry with extensive expertise in neuroimaging of human populations and over 100 peer publications. Dr Mauricio Tohen, Chair and Professor of Psychiatry, is an international expert in the treatment of psychotic disorders and has over 300 peer reviewed publications. These three clinician scientists have been working together in the UNM Psychiatric Center (UPC) EARLY First Episode Clinic for the past 5 years. William Wylie, MD is a 4th year psychiatric resident at UNM in the Psychiatry Research Track. He has been mentored by Dr. Bustillo and Dr. Nick Mellios PhD, form the Department of Neurosciences, in the application of circRNA measurement in psychiatric populations. Clinical research staff – Crystal Garcia has extensive experience (5 years) in recruitment, consent procedures, and clinical/cognitive assessments in psychotic and healthy control populations including all the tools proposed for this study. Analysis staff include Crystal Garcia and Haiyan Zhu, a PhD candidate from the UNM Department of Mathematics and Statistics, who are experienced in neuroimaging processing.

9.2. When applicable, describe which licensed physicians/providers will be responsible for medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics.

Drs. Bustillo, Lenroot, Tohen and Wylie will be the licensed psychiatrists responsible for the psychiatric care of the patients with psychotic disorders.

9.3. Describe other resources available to conduct the research: For example, as appropriate:

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

Recruitment of 35 subjects in their first episode of psychosis (as defined above) is feasible within two years. Dr. Bustillo, Dr. Lenroot and Dr. Mauricio Tohen are the lead psychiatrists for the EARLY First Episode Clinic at the UPC. This clinic has been receiving referrals for this specific population for the past 8 years. Last year, we enrolled 30 such patients. Our experience with neuroimaging of psychosis patients over the past 20 years support that over 50% of such patients will be agreeable to research. We have expanded our sources of referrals throughout the state and expect the numbers for 2022-2024 will increase by at least 25%. Hence, we are confident we will recruit the 35 psychotic patients as proposed. Finally, our group has ample experience recruiting HVs subjects from the Albuquerque community.

- *Describe the time that will be devoted to conducting and completing the research.*

The time that will be devoted to conducting and completing the subject recruitment and data acquisition is 2 years. Another year will be devoted to completing analyses.

- *Describe the facilities available to conduct the research.*

The Center for Psychiatric Research has enough space to conduct the clinical interviews, cognitive assessments, and neuroimaging analyses. MRN has the hardware and software resources to collect the MRI data. We have repeatedly used these 2 facilities over the past 15 years to conduct neuroimaging research in this population.

- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*

All patients with a psychotic disorder will be seen weekly for the 12 weeks of the study by a research psychiatrist to assess and address their medical and psychological needs.

- *Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

Our team (psychiatrists, clinical research assistant, and neuroimaging research assistant) have been working together in neuroimaging and pharmacological studies in early psychosis for the past 20 years. All personnel will be familiar with the study protocol. Our group meets weekly for 1 hour to go over our studies and will continue to do this once the present study is under way. The PI (Bustillo) will

be responsible that each person is trained in the specific procedures that they are entrusted to execute (see Table of Events).

- *If CTSC resources are being accessed, Please provide the IRB submission and approval deadline dates on the CTSC Submission page in Huron IRB.*

Not applicable

10. Prior Approvals

10.1. Describe any approvals that will be obtained prior to commencing the research. (e.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Approval by MRN will be obtained prior to commencing of research. IND exemption for use of lumateperone for Bipolar-I mania/mixed episode with psychotic features, schizophreniform, schizoaffective, Delusional or Psychosis Not Elsewhere Classified disorders from the FDA has been approved.

10.2. Upload the required Departmental Review Form signed by your Department Chair (or authorized designee if the PI is the Department Chair) into Huron IRBunder "supporting documents." DONE

10.3. If a study includes ionizing radiation, the Radiation Safety Attachment (HUS-FORM_1) must be uploaded (attached) in Huron IRBwith your submission. The consent should include radiation exposure information in the Risks section.

N/A

10.4. If applicable to the study, include the signed "Biological Specimens" and/or "Drug Attachment" in Huron IRB with your submission.

11. Multi-Site Research

11.1. If this is a multi-site study where the UNM HSC PI is the lead investigator, or UNM HSC is the coordinating site, describe the processes to ensure communication among sites, such as:

N/A

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators will conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

11.2. Describe the method for communicating to engaged participating sites:

- *Adverse events*
- *Problems*
- *Interim results*
- *Data and safety monitoring reports*
- *The closure of a study*

11.3. If the UNM HSC investigator is serving as the "sponsor-investigator" of a FDA-regulated trial, describe how sponsor responsibilities will be fulfilled, including, but not limited to:

- *Trial Monitoring*
- *Investigational Product Accountability*
- *Safety and other interim reporting to investigators and FDA*
- *Unanticipated Problem reporting to investigators, IRBs, and FDA*

N/A

12.Study Procedures

12.1. List any collaborating site where human subject research will be performed and describe the role of those sites and collaborating investigators in performing the proposed research (if applicable)

Research visits will be performed at UNM Center for Psychiatric Research (interviews, ratings, urine drug screens, medications dispensation, and pregnancy tests), the Mind Research Network (MR imaging) and the Tricore lab (blood draws for subjects). Due to the increased risk of exposure to coronavirus additional steps will be added to the study procedures in an effort to minimize transmission of COVID-19.

Prior to in person study visits: Participants or potential participants will be contacted by phone the day before the study visit and asked about any recent illness, exposure to others who are ill, or travel to high risk areas (see Covid Screening Sheet). If any of the previous apply, the participant will be asked to reschedule. If none of the above apply, participants will be asked to bring a face covering to be worn during the visit. Potential participants that do not require a legally authorized representative to be present for consenting, will be informed that anyone who accompanies them will be asked to come back when the visit has ended or to wait outside of the building.

During in person visits: When the participant arrives, their temperature will be taken with a touchless thermometer. If they are running a fever (temp > 100F), they will be asked to come back at another time and will be called to reschedule. Study staff will have wiped down any surface or materials that will come in contact with themselves and participants before and after use. Study staff will also wash their hands frequently, use hand sanitizer, wear a

mask, and maintain 6' social distance whenever possible. If the study team member is within 6' of the participant, a face shield will be worn. Participants will also be asked to wash their hands or use hand sanitizer when going between study related tasks as well as wear a mask and social distance when possible. Disposable masks will be available for participants who do not have or forget their face coverings.

Cleaning between participants: After participants leave, spaces and materials will be wiped down and disinfected.

12.2. Provide a thorough description of all study procedures, assessments and subject activities in a logical and sequential format.

See attached Table of Events and 12.5 below

12.3. For studies that collect existing or prospective data, describe the source of information, whether collected prospective or retrospectively

Prospective clinical, cognitive, neuroimaging, and blood metabolic data will be collected from patients with first episode psychosis per protocol in attached Table of Events. In healthy volunteers only cross-sectional clinical, neuroimaging, a blood sample, and cognitive data will be collected.

12.4. Indicate what study activities happen when and where.

See above 12.1 and attached Table of Events.

12.5. Describe, in chronological order, all research procedures and interventions being performed and when they are performed. Include:

- *Each specific intervention, procedure, examination, imaging, laboratory test, etc. that subjects will undergo for the purposes of the research and the purpose of it.*

Magnetic Resonance Imaging (MRI): Two MR scans at rest (ie: no cognitive task) will be performed: one before randomization and the second one 6 weeks after blinded treatment with all patients. However, healthy volunteers will only have one MR scan. The MRI technician will perform each scan acquisition which includes: structural MR, diffusion tensor imaging, rest functional MR, 3-D MR spectroscopy, and neuromelanin MR. This takes between 55 and 60 minutes.

Advancement of the second MR scan: If patients experience any significant persistent intolerance to the assigned treatment (e.g.: parkinsonism that does not improve with benztropine or akathisia despite treatment with propranolol or lorazepam), their initial medication will be blindly switched to the alternative anti-psychotic. If the blinded medication switch occurs at or after 3 weeks of treatment with the original drug, the end of study MR scan (and other assessments) will be advanced to be completed as close as possible to the date of switching medications. If the switching occurs before 3 weeks of treatment, the end of study MR scan (and other assessments) will take place as planned, after a

total of 6 weeks of blinded treatment (the goal is to ensure the maximum length of exposure to a particular well tolerated antipsychotic before the end of study assessments are implemented). If the patient's psychotic symptoms are not responding as expected, the blinded medication will be gradually increased (up to 4 tab per day). However, if lack of response persists, the research psychiatrist will also have the option to switch the medication blindly. End of study assessments will be advanced as when switching due to medication intolerance.

Laboratory tests for FEP: All patients with psychotic disorder will have the following tests:

- CBC, TSH, liver panel, Chem-7 and urinalysis (only at baseline for medical clearance before randomization; these are not research measures).
- Fasting lipid panel, blood sugar and serum prolactin twice, at baseline and at 6 weeks (or when final visit is advanced; these are secondary outcome measures, per Aim 2)
- Whole blood for circRNA profiling will be collected using a PAXgene Blood RNA tube at baseline and at 6 weeks. The samples will be de-identified and linked with study participants via a unique identifier. RNA will be purified using a PAXgene Blood RNA Kit or a PAXgene Blood miRNA Kit, per the manufacturer's instructions. RNA quality and concentration will be assayed through Nanodrop 2000 spectrophotometer and Qubit 3. RNA will be used for circRNA array profiling (Arraystar) as well as validation with circRNA-specific qRT-PCR.
- All subjects will have a urine drug screen before each MR scan.
- All female subjects will have a urine pregnancy test before each MR scan.

Laboratory tests for healthy volunteers:

- Each subject will have one blood sample collected for circRNA.
- All female subjects will have a urine pregnancy test before the MR scan.

Antipsychotic drugs for psychotic patients:

We will use 2 antipsychotic drugs, lumateperone and risperidone, FDA approved for psychotic symptoms, specifically in schizophrenia and bipolar-I disorders. The other less common disorders included (schizophreniform, schizoaffective, delusional, and unspecified schizophrenia spectrum and other psychotic disorders) are usually temporary diagnoses that most often will end up as schizophrenia or bipolar-I. So strictly speaking, use of risperdone and lumateperone will be off label for these less common diagnoses. However, all of these other diagnoses are also treated with antipsychotic drugs per standard of care. This investigation

involves a small pilot randomized controlled study of the two antipsychotic agents. Antipsychotic drugs are the treatment of choice for patients experiencing their first psychotic episode (Marder et al, NEJM, 2019). Risperidone and lumateperone are FDA-approved for schizophrenia. Antipsychotics are also widely used for bipolar-I with psychotic features, despite many of them not being FDA-approved (McIntyre et al Lancet. 2020). For example, in bipolar-I, manic with psychotic features, haloperidol (not FDA-approved for Bipolar-I) was shown to be just as effective as olanzapine, which has FDA approval (Tohen, et al. AGP 2003). Risperidone is also approved for Bipolar-I with mania/mixed episodes and lumateperone for Bipolar-I with depression. Hence, we will request an IND exemption for the use of lumateperone for BP-I mania and mixed episodes with psychotic features, schizophreniform, schizoaffective, delusional, and unspecified schizophrenia spectrum and other psychotic disorders). The study does not examine the efficacy or tolerability of these agents which are well described in the literature. The study does examine possible biological correlates of efficacy (brain glutamate and neuromelanin) and tolerability (serum prolactin and lipids). Hence, no therapeutic or diagnostic procedures are proposed.

- *Each survey, questionnaire, interview, focus group, etc., that subjects will be asked to complete or participate in for the research and the purpose of it.*

  For Psychotic patients and healthy volunteers:

  - Screening for inclusion/exclusion criteria by phone or in person by clinical coordinator, PI or Co-investigator (approximately 5-30 min).
  - A potential participant without an official diagnosis, but with symptoms suggestive of a psychotic disorder and who consents to participate, will be evaluated by the research psychiatrists; if he/she meets an appropriate diagnosis, he/she can consent for the study.
  - Informed consent: In person by clinical coordinator, PI or Co-investigator (30-60 min) or via zoom/REDCap when possible. Participants will be emailed an electronic copy of the consent form prior to the scheduled consenting visit. Participants will also be emailed a link to the HSC REDCap where the consent form is laid out in the same way as the PDF version they were previously sent but with the addition of places for initials and signatures. Participants can download a signed version of the consent form after all of the signatures have been put into the REDCap page.
  - Structured Clinical Interview SCID (DSM-5); this will include, if subject agrees, collateral in person or phone information from family members or friends. These will be contacted by phone, zoom or interviewed in person by the research staff or PI after the subject

consents to their participation. A consent script will be used prior to gathering any collateral information from family members/friends (see Consent-Survey-Research_Lumafep document). The family member/friend will be asked some questions from the SCID that are relevant to clarify information provided by the subject.

- Demographics (age, gender, ethnicity, etc.)
- Medication/medical history
- Fagerstrom (smoking data)
- Neurocognitive testing: the MATRICS battery, the standard in psychosis research, is an overall neurocognitive outcome and will be collected in all subjects once. The MATRICS evaluates several domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning & problem solving, and social cognition. It will be collected once at baseline in HV and once at the end of 6 weeks of treatment in FEP (so that it better reflects the underlying cognitive capacity apart from the impact of acute psychosis).

For Psychotic patients only, during the 6 weeks of randomized treatment:

- Calgary Depression Inventory (weekly)
- Young Mania Rating Scale (YMRS; weekly)
- Schizo – Bipolar Scale (once at baseline)
- Clinical Global Impression Scale (CGI; weekly)
- Abnormal Involuntary Movement Scale (AIMS; every 2 weeks)
- Simpson –Angus Scale (SAS; every 2 weeks)
- Barnes Akathisia Scale (BAS; every 2 weeks)
- Positive and Negative Symptom Scale (PANSS; weekly)
- Functional outcome will be assessed with the Specific Levels of Functioning scale (SLOF; Schneider et. al. Soc Work Res 1983). The SLOF is administered to the caregiver or clinician of a psychotic patient and examines 6 domains: personal care skills, physical functioning, interpersonal relationships, social acceptability, activities of community living and work skills (baseline and after 6 weeks).
- Suicide scale (CSSRS; every 2 weeks)
    - The FEP subject will be seen weekly and be formally assessed for suicidality every 2 weeks (standard of care at UNM Psychiatric Center is every 6 months). Because a research psychiatrist will be seeing subjects weekly, any indication of suicidality will be fully

evaluated by the clinician and appropriate measures (referral for hospitalization, more frequent assessments, involvement of family members) will be implemented.

- Weekly counts of capsules in returned bottles.

- *Each data source that will be used to gather information about subjects and the purpose of it (confidentiality will be addressed later.*

UH clinical records will be reviewed with HIPPA compliance to clarify psychiatric and medical comorbidity.

Notes in UNM Hospital record: During each of the six Study-Medication and the four Follow-up visits, the research psychiatrist will add a note in the patient's UNM hospital medical record briefly describing how she/he is responding to the research treatment. This information, that does not break the blind, may still be helpful to hospital physicians who may come in contact with the patient during the course of the study.

- *Indicate whether subjects would already be expected to undergo any of the procedures for clinical, diagnostic, or other non-research purposes*

Treatment with antipsychotic drugs are the mainstay therapy for this clinical population; likewise, clinical psychiatric examination and assessment of psychotic and other symptoms and side-effects are also expected procedures (however the SCID-5 and various ratings scales are more in depth than standard clinical practice). The baseline laboratory (CBC, TSH, liver panel, Chem-7, and urinalysis) as well as the repeated lipid panel and blood sugar are expected for patients being treated with an antipsychotic. Serum prolactin is measured in patients who develop galactorrhea or amenorrhea secondary to antipsychotics but is not an expected test for most patients. A structural MRI of the brain is very often requested in patients in their first episode of psychosis to rule out structural brain lesions. However, the majority of the MR imaging acquired (^{1}H-MRS, DTI, f-MRI and neuromelanin MR) are only for research purposes. Likewise, the MATRICS neurocognitive battery is only for research purpose.

- *Include all referenced study instruments, such as questionnaires, scripts, diaries, and data collection forms with your submission as separate attachments.*

Done

- *For HUDs, provide a description of the device, a summary of how you propose to use the device, including any screening procedures, the HUD procedure, and any patient follow-up visits, tests, or procedures. Note whether the HUD is being used for clinical purposes only or if you are proposing to study the safety or effectiveness of the device.*

N/A

13.Data Analysis

13.1. Describe the data analysis plan, including any statistical procedures.

Aim 1: Hypotheses 1a. For the group treated with *Lumateperone,* in a multiple regression model, the dependent variable *Efficacy* (difference in PANSS positive symptom score between baseline and 6 weeks) will be related to two independent variables: *Dopamine Change* (difference in bilateral S-N neuromelanin between baseline and 6 weeks), and *Glutamate Change* (difference in medial cingulate glutamate between baseline and 6 weeks), controlling for baseline PANSS positive symptom score and for compliance with medication treatment. Hypotheses 1b. For the group treated with *Risperidone,* in a multiple regression model, the dependent variable *Efficacy* will be related to *Dopamine Change* but not to *Glutamate Change,* controlling for baseline PANSS positive symptom score and for compliance with medication treatment. We will also use a multiple regression model on the baseline data to examine the difference between the FEP and HV with reference to the glutamate and dopamine in the medial cingulate and bilateral S-N, respectively.

Aim 2: Hypotheses 2a. In a multiple regression model, the dependent variable *Extrapyramidal side-effects* (difference in SAS score between baseline and 6 weeks) will be more strongly related to *Prolactin Change* (difference in serum prolactin between baseline and 6 weeks) in the *Group* treated with risperidone than the one treated with lumateperone, controlling for anticholinergic treatment and for compliance with antipsychotic medication treatment. Hypotheses 2b. In a multiple regression model, the dependent variable *Weight* (difference in subject weight between baseline and 6 weeks) will be more strongly related to *Lipid Change* (difference in serum lipids between baseline and 6 weeks) in the Lipid Change (difference in serum lipids between baseline and 6 weeks) in the *Group* treated with risperidone than the one treated with lumateperone, controlling for anticholinergic treatment and for compliance with antipsychotic medication treatment.

Aim 3: In an exploratory framework, differential expression of circRNA species will be assessed by t-test with Bonferroni correction for multiple comparisons.

Dr. Tohen will not be involved in the analysis of any of the end point data per his management plan with HSC COI.

13.2. Provide a power analysis, if applicable.

This is truly a pilot study, so there is no preliminary or previous literature available to suggest the strength of the relationship between any changes in glutamate or neuromelanin and changes in psychotic symptoms with any antipsychotic treatment. Hence, no power analysis is presented. However, with the small sample collected, we expect to calculate effect sizes for these relationships to design a well powered future study.

14.Provisions to Monitor the Data to Ensure the Safety of Subjects

This section is required when research involves more than Minimal Risk to subjects. Describe:

This study is a clinical trial that involves MR scans, blood work, clinical ratings and neurocognitive assessments, all with minimal risks. Patients with psychosis will be randomly assigned to treatment with an FDA approved antipsychotic as per standard of care. Both risperidone and lumateperone are FDA-approved for the diagnoses of schizophrenia and bipolar-I disorders. Lumateperone, is the most recently approved antipsychotic in the U.S., and although it has a particularly benign extrapyramidal and metabolic profile in short term studies (Correll et al, JAMA Psych, 2020), there is less information on its long-term tolerability. Patients will be seen weekly by the treating research psychiatrists to monitor response and tolerability (more frequently than the 4 to 12 weeks which is standard of care locally). Though blinded, the protocol is flexible enough to allow drug titration, addition of standard medications for extrapyramidal side-effects or insomnia, and switching to the alternate antipsychotic agent. Our group has safely implemented previous controlled trials with MR imaging in this populations (Bustillo et al, NPP 2008; Bustillo et al. Mol Psych 2010). Any reportable events will be submitted to the HRPO within 5 days.

The PI, Dr. Bustillo, will have overall responsibility for monitoring the trial. He will meet at least weekly for about 1 hour with the rest of the study team to go over specific issues relevant to enrolled subjects as well as review overall procedural implementation. He has 25 years of experience doing neuroimaging research in the context of clinical trials with this population at UNM Psychiatric Center (UPC) and 17 years in collaboration with the Mind Research network (MRN). He has over 150 peer reviewed publications and multiple intra and extramural funding awards.

14.1. *The entity (e.g., DMC, DSMB) or individuals (e.g., medical monitor) who will perform data and safety monitoring. Describe whether they are independent of or affiliated with the sponsor or investigator. If a DMC or DSMB is planned, describe the composition of the committee or board. Generally, a DSMB or DMC should be composed of experts in all scientific disciplines needed to analyze and interpret the data (e.g., epidemiologists, biostatisticians, subject matter experts).* N/A

14.2. The safety information that will be collected and monitored.

We will be collecting the SMARTS for monitoring side effects and the CSSRS for monitoring suicidality.

14.3. The frequency or periodicity of review of data, such as specified points in time or after a specific number of participants have been enrolled. N/A

14.4. The plans for review of scientific literature and data from other sources that may inform the safety or conduct of the study. N/A

14.5. *The procedures for analysis and interpretation of the safety data.*

The new safety data for subjects actively in the study will be discussed at the individual subject level weekly by the PI and research staff. Hence, if a

subjects' suicidality or side-effects have increased, this will be discussed amongst the research psychiatrists who are expert clinicians. The psychiatrist treating the subject will elaborate on what changes in treatment were implemented the day of the last visit (when safety indices worsened) and any potential new changes considered for the next visit. This goes beyond the standard of care in the community, were clinicians see patients every several weeks and do not regularly discuss safety changes with colleagues. There will not be planned analyses of safety data before the study is completed since we will not have a Data Safety Managing Board (DSMB). This is justified because this is minimal risk study, which uses two FDA approved medicines with well defined risks. We have no expectations that our small (N=25 patients) will provide any new valid safety findings that might justify interim analyses as is typical with a DSMB.

14.6. The conditions that would trigger a suspension or termination of the research (i.e., stopping rules), if appropriate.

We do not expect an increase in morbidity or mortality beyond what is expected for this population as per standard or care (this is a minimal risk study). Hence, we have no specific provisions that would result is stopping the whole study.

14.7. The plan for reporting findings to the sponsor, investigators, and HRRC.

Any reportable events will be submitted to the HRPO within 5 days. The sponsor will not receive reports as this is an investigator initiated study and they do not request this information.

15. Withdrawal of Subjects

15.1. Describe any anticipated circumstances under which subjects may be withdrawn from the research without their consent.

The PI reserves the right to terminate the study at any time. Reasons for the study termination may include: successful completion of the study; the required number of subjects has been recruited; failure of study investigators to comply with the protocol or GCP guidelines; safety concerns; positive urine drug screen; inadequate recruitment of subjects, etc. Subjects may choose to stop study participation at any time. If the study doctor feels that participation is not in the patient's best interest, he may choose to stop the study. Subjects who are deemed to be uncooperative or who provide false information will also be terminated from the study. Subjects who receive abnormal scan findings by the neuroradiologist will be dealt with on a case-by-case basis. Any new information that arises with regard to risks of the various neuroimaging modalities could also lead to study termination.

15.2. Describe any procedures for orderly termination/safe withdrawal (e.g., tapering of meds, physical exams, laboratory or other tests, etc.).

If a patient randomized to study drug wants to terminate participation they will meet with the research psychiatrist within a week of their decision. Then they will jointly

plan transition to another anti-psychotic agent as per standard of care. Neither of the study drugs need to be tapered down (lumateperone is dispensed as a single dose, risperidone has a long half life and a narrow dose range). In this case the blind will be maintained unless the patient experiences a serious anaphylactic reaction. The psychiatrist will continue to meet the patient as per standard of care until they are clinically stable or they have been transferred to an available local patient care provider. No additional lab work is indicated during this withdrawal process.

15.3. Describe any procedures for partial withdrawal (e.g., from procedures but allowing continued data collection by record review, phone contact, etc.).

N/A

15.4. Describe the disposition of existing data/specimens when a subject withdraws. Describe any restrictions on a subject's ability to withdraw any already gathered data or specimens (e.g., unable to retrieve because it has been stripped of identifiers and no code exists to allow re-linking). (Note: FDA requires that existing data be maintained for studies subject to FDA oversight.)

The participant can withdraw from the study at any time and no new data will be collected. However, data collected up until that time may still be used by the investigator for appropriate analyses. If a participant with a LAR who has assented to participate (and the LAR has consented) wants to withdraw, participation in the study will be discontinued.

15.5. Describe withdrawal procedures and any limitations in the consent document.

Done.

16.Data Management/Confidentiality

16.1. If data or specimens will be transferred/shared with an external entity (institution, company, etc.), please complete Checklist sections 47 and 48, as applicable.

N/A

16.2. Indicate how the research team is permitted to access any sources of information about the subjects.

The research team will request for each psychotic disorder participant to sign a HIPPA form to access PHI to support diagnosis, treatment and co-morbid conditions.

16.3. Note whether the research requires the access, use, or disclosure of direct identifiers (e.g., name, medical record number, etc.)

Yes

16.4. Several zip codes are below the 20,000-census mark, and HIPAA regulations require that the three first digits of the zip code are replaced with "000" in order to create a de-identified data set. Based on the 2010 Census, the sparsely populated zip codes in New Mexico are as follows: 878, 879, and 884 pre-fixes. Please indicate if these zip codes will be included, and if so, indicate

they will be replaced with "000" in order to create a de-identified data set. If utilizing these zip codes, the data set would be a limited data set.

The sparsely populated zip codes may be included for a minority of subjects and they will be replaced with "000" as requested.

16.5. Note whether the research requires the access, use, or disclosure of Protected Health Information.

Yes (as above).

16.6. Note whether the data is publicly available.

No

16.7. Note whether the data includes information that may be considered sensitive or require additional protections such as HIV, genetic test results, mental health information, substance abuse information, criminal records, etc.

Yes.

16.8. Indicate whether a Certificate of Confidentiality (CoC)will be used to protect data from forced release (e.g., subpoena) and whether the certificate is in place or will be applied for once IRB approval is in place. Please note: NIH funded studies are automatically covered under a CoC. More information on Certificates of Confidentiality is available here: http://grants.nih.gov/grants/policy/coc/index.htm

No

16.9. Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption in transmission and at rest, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, transmission and transport. Please note: direct input of data into an IT created restricted folder on a UNM HSC departmental drive is the recommended method, if possible. The REDCap system is also considered a secure method for data collection and maintenance during the life of the study. Also note that multi-factor authentication (MFA), which REDCap supports, is recommended.

Every effort will be made to protect the confidentiality of participants' records. However, complete confidentiality of records cannot be guaranteed as records may be examined by authorized personnel from the UNM Human Research and Review Committee. Participants will be informed of this possibility prior to signing the consent forms. Otherwise, records will be kept strictly confidential and will not be inspected by any other agency unless required by law. Behavioral and computerized data from the MRI scanning sessions will not contain participants' names or any other identifying information per HIPAA requirements. Data will be de-identified as appropriate to the UNM Human Research and Review Committee and HIPPA requirements by assigning a randomized eight-digit number (URSI) to each participant upon entry into the study. This number will be used for all correspondence

between study investigators and all data collection and analysis after the initial screening visit. MRN has a state-of-the art IT network with all necessary security mechanisms in place. Any personal information entered into computers is password protected and monitored for suspicious activity. In order to contact subjects for telephone visits and/or other matters, it will be necessary to retain names and telephone numbers of active subjects. However, these direct identifiers will not be stored with any clinical data or subject information in order to protect confidentiality. Any direct identifiers will be stored in locked cabinets, on a secure MRN server, and/or the COINS database on a secure HIPAA compliant server, separate from any clinical data. These will only be accessible by key study personnel. A link between study code numbers and direct identifiers will be retained in order to contact subjects for visit appointments or at a later date to inform them of newly received information. This link will be retained for the duration of the study. Subjects will be identified only by unique Patient ID numbers in Case Report Forms (CRFs) and electronic CRFs. The CRFs will be maintained in a locked cabinet housed in the Center for Psychiatric Research. These documents will only be accessible by authorized study staff and will comply with HIPPA requirements for the storage of health information. Moreover, all information will be in double-locked rooms per HIPAA specifications. At the time of study closure, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in radiological scans and reviews. The results of this research may be presented at meetings or in publications; however, participants' identity will not be disclosed. The participant will be provided with a copy of the consent form to take home. Study record will be maintained for six years after the study closes after which the records will be destroyed per federal regulations.

16.10. If data will be coded, describe the nature of the code and mechanisms that will be used to protect the code (e.g., secure storage, limited access, separate location from research data).

See 16.9

16.11. Describe any procedures that will be used for quality control of collected data.

All clinical, demographic, lab work, and cognitive data will be double entered into the COINS database by study personnel. The neuroimaging data will go through extensive standardized data quality procedures established at MRN.

16.12. Describe the following:

- *What information will be included in that data or associated with the specimens?* See 16.9.
- *Where and method of data storage and how will it be maintained in a secured manner (i.e. encryption, password protection, REDCap, etc) and*

- *Method in which data will be collected and stored (i.e. electronic, hard copy, specimen, etc)?* See 16.9.
- *How long the data or specimens will be stored?* See 16.9.
- *Who will have access to each method of data or specimens* See 16.9.

16.13. How data and specimens will be transported. Describe if data will be collected, transmitted, and/or stored via the internet, the identifiability of the data, and the security measures that will be employed to protect it (if data is de-identified, explicitly state that).

Most blood and all urine specimens will be analyzed where collected and will not be transported. The blood sample for circRNA will be transported by a research staff member from the UNMH Tricore lab (patients) to the UNMHSC neurosciences. Data will be maintained in the COINS network and will not be transported. Regarding identifiability and security of data see 16.9.

16.14. Describe if data will be collected by audio or video recording, how the recordings will be secured, whether and when recordings will be transcribed, if the transcription will include identifiers, if, when, and how the recordings will be deleted. Describe if the subjects will have the opportunity to review the recordings and request full or partial deletion. If the recordings may include persons other than the subjects, describe how this will be managed.

N/A

16.15. Describe if the data will include photographs, what will be included in the photographs, and how the photographs will be secured. Describe if subjects will have the opportunity to review the photographs and request destruction. If the photographs may include persons other than the subjects, describe how this will be managed.

N/A

16.16. State how long research record will be maintained. Note: Federal regulations require that research records will be maintained for at least 3 years after study completion.

See 16.9.

16.17. Research records of minors (under 18) must be retained until the minor turns 22 years old per the following policy: HSC-R-801 PR.1 "Research Data and Materials Retention Policy".

N/A

16.18. HIPAA Requirements: Any research that involved collecting identifiable health information is subject to HIPAA requirements. As a result records must be retained for a minimum of 6 years after each subject signed an authorization.

Records will be maintained for a minimum of 6 years after study completion then destroyed.

17.Data and Specimen Banking

17.1. If data or specimens will be banked or archived locally for future use, provide the name and study number of the repository that they will be deposited into. Describe exactly what data or specimens will be banked and for what purposes, and whether the data or specimens will include identifiers, be coded, or be fully stripped of all identifiers with no code or key that would allow relinking. Be certain to describe the banking in the primary consent. A separate consent and authorization, if applicable, will be necessary for the banking activity itself and is typically provided by the repository. If you need to establish a repository for the purposes of banking or archiving data or specimens, a separate submission for the repository is needed as this is considered to be a distinct research activity under the regulations.

Early Psychosis Data Repository: The Early Psychosis data repository (HRRC #19-179) will be used to store their baseline demographic and clinical information collected from consenting FEP subjects who agree to have their information stored in the data repository (no neuroimaging or bloodwork data will be stored). This centralized database will store information for future unspecified use. In doing so, this will allow for a less burdensome and more efficient process for collecting information routinely utilized by all researchers. Consent for data to be included in the repository will be obtained during the consent process. Data will be stored for 20 years at which time the electronic repository and the database will be cleared.

If this is a multi-center study, and/or if data or specimens will be banked or archived elsewhere, identify who the holder of the data or specimens will be, exactly what data or specimens will be banked and for what purposes, and whether the data or specimens will include identifiers, be coded, or be fully stripped of identifiers with no code or key that would allow relinking. A Materials Transfer or other agreement may be necessary, please consult with the HSC Sponsored Projects Office at 505-272-6264 or by email at hsc-preaward@salud.unm.edu. Material Transfer Agreement procedures may be found at http://hsc.unm.edu/financialservices/preaward/ancillary-agreements/material-transfer-agreements/procedures.html. Be certain to describe the banking in the consent and authorization, using opt-in procedures, and the procedures for subjects to request withdrawal of their data or specimens and any limitations on their ability to do so.

N/A

Data will be stored in locked cabinets at the UNM Center for Psychiatric Research. Subjects' charts will be stored without direct identifiers. Only approved research staff on Dr. Bustillo's team will have access to these records. Other than the research team, the study sponsor and the HRRC will be permitted access to the records. In order to contact subjects for telephone visits and/or other matters, it will be necessary to retain names and telephone numbers of active subjects. However, these direct identifiers will not be stored with any clinical data or subject information in order to protect confidentiality. Any direct identifiers will be stored in locked cabinets and in the

COINS database on a secure HIPAA compliant cloud-based server, separate from any clinical data. These will only be accessible by key study personnel. A link between study research ID numbers and direct identifiers will be retained in order to contact subjects for visit appointments or at a later date to inform them of newly received information. Collected data will be labeled with initials and a unique researcher subject identifier (URSI) which will be entered and stored in the COINS database on a secure HIPAA compliant cloud-based server. Data linking scan to identity will be maintained at the Mind Research Network indefinitely allowing the neuroradiologist to compare future scans with previous ones. The approved study team members may be able to access existing scan and neuropsychological data from individuals who have been recruited from other studies. Only subjects who have given permission for their previously collected data to be shared with the current study will be included on a case-by-case basis in order to reduce the number of times the same tests have to be performed. Clinical and research data will be de-identified after the study is complete. After that period, the link between clinical and research data will be deleted. The de-identified data will be kept indefinitely.

18. Risks to Subjects

18.1. List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Describe the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. Note that almost all research includes the risk of a breach of confidentiality and/or privacy.

See below.

18.2. If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

N/A

18.3. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If pregnancy testing or birth control provisions are required, describe these.

All female subjects will be screened for pregnancy at the beginning (baseline) and end (6 weeks) of the study.

18.4. If applicable, describe risks to others who are not subjects.

N/A

18.5. Describe the steps being taken to minimize the probability or magnitude of risks.

See below.

Note: All risks described here should also be described in the consent document.

The following section describes the risks (18.1) as well as the steps to minimize these (18.5).

Pharmacotherapy: Patients with a first episode psychotic disorder (FEP) will have a clear indication for antipsychotic therapy as per standard of care. They must have active psychotic symptoms (score of 3 or higher in any of the 7 items of the positive symptoms scale of the PANSS) and hence will be randomized to treatment with therapeutic doses of either of two FDA approved antipsychotic agents: lumateperone (single dose 42 mg/day, as per FDA) or risperidone (target dose between 1 to 4 mg/day). The dose range of risperidone is based on its mean modal effective dose determined by the Clinical Antipsychotic Trials of Intervention Effectiveness (Lieberman et al, NEJM, 2005) and its well-characterized efficacy and safety profile as one of the most prescribed antipsychotics in the United States. Both lumateperone and risperidone have similar side-effect profiles which include: extrapyramidal (tremors, stiffness, restlessness, dystonia, dyskinesia), metabolic (weight-gain, dyslipidemia, hyperglycemia, increased prolactin) and general (sedation, dry-mouth, dizziness and nausea; Correll et al, JAMA Psych 2020). The limited data available from direct comparison suggests that extra-pyramidal and metabolic side-effects may be less frequent with lumateperone (Correll et al, JAMA Psych 2020). A very serious, life-threatening but rare complication of treatment with all antipsychotics is neuroleptic-malignant syndrome (NMS; in 25 years of practice in UNM-HSC, the PI has seen 2 cases, both in chronically treated patients). Likewise, all antipsychotic agents can cause tardive dyskinesia, a serious chronic movement disorder that may occur usually after months or years of treatment (current study is for 6 weeks). FEP subjects will be evaluated by a research psychiatrist every week to carefully monitor tolerability and response to blinded treatment. If side-effects are present, the psychiatrist may lower the antipsychotic dose or blindly switch to the alternative antipsychotic. Additionally, she/he may add the following open-label agents as per common practice: a) benztropine 1- 4 mg/day (for parkinsonism or dystonia); b) lorazepam 1-4 mg/day (for akathisia, anxiety or insomnia); c) propranolol 20-120 mg/day (for akathisia); and d) trazodone 50 to 200 mg/day for insomnia. These supplemental medicines will not be provided by the research pharmacy as part of the study. The subject will get a regular prescription to fill at his/her local pharmacy. After up to 6 weeks of blinded treatment, patients will be transitioned to open-label antipsychotic treatment with lumateperone (provided by study sponsor free of cost for up to 6 months) or to any other agent as per standard of care (for which the patient will be responsible to pay for). Patients will be seen weekly for 4 weeks by the research psychiatrist for stabilization on the selected open-label treatment before being referred back to a community-based provider of the patient's choosing. Any other therapies, pharmacological and psychosocial, that are consistent with the standard of care will also be recommended to the subject during this transition phase.

Exacerbation or persistence of psychotic/manic symptoms: Per inclusion criteria, all FEP subjects will have psychotic symptoms which are expected to benefit from blinded antipsychotic therapy. Subjects with bipolar-I disorder may also have manic symptoms (e.g.: euphoria, irritability, grandiosity), depressive (sadness, hopelessness, anhedonia) or mixed symptoms. These symptoms are also commonly treated with antipsychotic drugs as per standard of care. Some antipsychotics actually have FDA approval for bipolar-I disorder. Risperidone is FDA approved for manic symptoms and lumateperone is approved for bipolar-I depressive symptoms. If the subjects were taking an antipsychotic agent before randomization, it will be gradually tapered off during the first week of the trial as per standard clinical practice, while the study medication is titrated. There will be no wash-out period. If the patient's psychotic/manic symptoms are not responding as expected, the blinded medication will be gradually increased (up to 4 mg of risperidone per day). However, if lack of response persists, the research psychiatrist will also have the option to switch the medication blindly or withdraw the subject from the study and recommend treatment with open-label medication. The transition period for 1 month, with weekly clinical visits will still be made available to the subject.

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. The MRI scan is non-invasive and considered minimal risk by the FDA and UNM Human Research Review Committee (HRRC). However, the scanner acts like a large magnet, so it could move ferrous containing objects in the room during the experiment. Patients will be screened to rule out the presence of metallic objects that may be in their bodies prior to the MRI scan. The MRI may also cause claustrophobia and anxiety from loud, banging noises made by the machine. Headphones and earplugs are provided for protection. Should a participant become claustrophobic during a scan, they can stop the scan at any time by speaking through the two-way intercom or squeeze a button that they hold in their hands throughout the entire scan. Support will be available to deal with any anxiety or fatigue associated with behavioral testing. A two-way intercom system and a video monitoring system provide continual monitoring of the subject's condition. If discomfort or concern is expressed or detected, the experiment will be stopped and the subject will be given the option to discontinue at any time. FEP subjects who are likely to become claustrophobic may be offered 1 or 2 mg of lorazepam by the research psychiatrist, to take 1-2 hrs before the scan. Participants will be asked to change into hospital scrubs prior to being placed in the scanner to ensure that they do not introduce any metallic object into the imaging environment. All participants will complete an MRI safety screening prior to being scanned to rule out any contraindications to receiving the MRI scan. There are no known health risks or long-term harmful effects associated with the MRI. However, since the effect of the MRI on early development of the fetus is unknown, participants

who are pregnant will not be allowed to go into the MRI. Females that are 18 years of age or older and there is a possibility of pregnancy, will be asked to take a urine pregnancy test before being allowed to participate in the study. The test results will only be shared with the participant.

Blood draw: Blood draws from a peripheral vein in the forearm will be drawn by a trained phlebotomist at the Tricore labs or at the CPR by Dr. Wylie or Ms. Garcia. This will cause mild discomfort, pain and the possibility of a temporary local bruise. The likelihood of local infection is extremely low as the area will be swabbed with disinfectant and the phlebotomist will wear sterile gloves.

Measurements of circRNAs will not involve whole genome sequencing. Hence there is no risk for potential health insurance discrimination.

General risks (uncommon): Participation in the study may result in discomfort, emotional stress, behavioral fatigue, and inconvenience. If the patient arrives in crisis or becomes very anxious or upset during the procedures, study personnel will contact the study doctor. The study doctor or other clinical or senior study personnel to make decisions regarding the suitability of embarking on study procedures on that day.

Confidentiality: Participants will be informed that project records will be kept in a locked and secure area. Complete confidentiality cannot be accomplished. However, confidentiality will be maintained by labeling assessments with only unique research code number (URSI) only instead of names. Project staff who have access to records are trained in procedures to maintain strict confidentiality, which includes a prohibition against removing records from the project area, and prohibition to divulge any information or revealing the identity of subjects without written subject consent. All project staff that will have contact with participants will have received research ethics training. Research staff will use “dip sticks” to analyze urine drug screens, thereby circumventing the need to send specimens to an outside lab where confidentiality might be breached.

Participants will be clearly informed of their right to withdraw from the study at any time and still receive full compensation for the time they have spent in the study at that point.

Risk of exposure to COVID-19: Due to the current global pandemic, there is an increased risk of exposure to the novel coronavirus by attending a public setting like the Psychiatric Research Center and the Mind Research Center. This is part of a “new normal” when going to any public setting. Study staff will follow State and Federal guidelines regarding social distancing, touch surface disinfecting, screening for symptoms of COVID-19, and wearing face

masks. Despite these best efforts for risk mitigation, there is always a chance of getting coronavirus whenever there is contact with people.

19. Potential Benefits to Subjects

19.1. Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Note: Compensation for research participation is not considered a benefit.

The potential benefits for participants in this study are minimal. Participants will likely improve in their psychotic symptoms with blinded treatment, since improvement in first episode psychosis is over 90 % with antipsychotic therapy. However, this should not be thought of as specific to the study since both drugs (lumateperone and risperidone) are available for prescription by any physician as part of the standard of care. Subjects may benefit from the MRI procedure, as abnormal findings on structural MRI scans will be read by a neuroradiologist. They will receive a radiology review and report of their MRI scan. This could lead to early detection of previously unknown abnormalities and even has the potential to be life-saving in some cases. Finally, for FEP subjects and if clinically-indicated as per the research psychiatrist, open-label lumateperone will be made available free of cost by the study sponsor for up to 6 months. No other benefit to participants is anticipated.

19.2. Indicate if there is no direct benefit. Do not include benefits to society or others in this section.

See 19.1.

Note: All potential benefits described here should also be described in the consent document.

20. Recruitment Methods

20.1. Describe when, where, and how potential subjects will be recruited.

See 20.3

20.2. Describe the methods that will be used to identify potential subjects (e.g., chart review, referral, etc.).

See 20.3

20.3. Describe materials that will be used to recruit subjects (e.g., emails, scripts, advertisements, brochures, flyers, etc.). Attach draft copies of the documents or audio or video recordings with the application. Once the draft has been approved, the final copy of the printed material, audio or video recording must be submitted for review and approval prior to implementation. Please see Worksheet HRP-315 for information on advertisement standards.

Participants will be recruited and screened directly by trained lab personnel once the study is approved by the HRPO and all the procedures are in place. Clinician referrals will be mainly from the UNM Psychiatric Center clinics and inpatient wards. Potential participants will be phone-screened or invited to come in for an initial screening interview at UNM Psychiatry Research Center. Clinicians who work at UNM psychiatric center will be informed about the study through flyers posted in the center, email messages with the flyers attached submitted through the department of psychiatry listserv, as well as word of mouth by the study research psychiatrists who are attendings at the center. At that time, a brief structured interview will be administered to evaluate the appropriateness of their participation. If potential participants meet the basic study criteria, participants will be invited to make an appointment to come to the Psychiatry Research Center, and undergo consent procedures and be enrolled into the study.

Healthy Volunteer subjects will be recruited and screened directly by trained lab personnel. Flyers, newspaper, and other media advertisements will be used if needed. A modification will be submitted as needed. Potential participants will be phone-screened or invited to come in for an initial screening interview at UNM Psychiatry Research. At that time, a brief structured interview will be administered to evaluate the appropriateness of their participation. If potential participants meet the basic study criteria, participants will be invited to make an appointment to come to the Psychiatry Research Center, undergo consent procedures and be inducted into the study.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. Describe the steps that will be taken to protect subjects' privacy interests. "Privacy" refers to persons and their interest in controlling the access that others have to themselves. For example, based on their privacy interests, people may want to control:

- *The time and place/setting where they are examined or provide information*
- *The nature of the information they provide*
- *The nature of the experiences they are exposed to*
- *Who may observe or have access to information about them*

For example, individuals may not want to be approached for participation, provide responses to a research interview, or undergo a research procedure in a location where they may be seen or overheard.

21.2. Describe the steps that will be taken to protect subjects' privacy including privacy protections during recruitment, consent, and data collection. Issues related to data are addressed in the Data Management/Confidentiality Section.

The following section addresses items 21.1 and 21.2.
In order to contact subjects for telephone visits and/or other matters, it will be necessary to retain names and telephone numbers of active subjects. However, these direct identifiers will not be stored with any clinical data or subject information in

order to protect confidentiality. Any direct identifiers will be stored in locked cabinets and in a password-protected database, separate from any clinical data. These will only be accessible by key study personnel. During the study visits at the Center for Psychiatric Research, there are three private, closed door assessment rooms that are available for research purposes. Subjects will be interviewed usually during working hours, between 8 am and 5 pm but these may change for the subject's convenience. Subjects will provide demographic (age, education, occupation, etc) and clinical information (psychiatric and medical history, psychiatric symptoms, medications, side effects, etc). This information will be collected in the context of a clinical research interview by trained staff. Only approved research staff may observe and have access to the information collected. During the two neuroimaging sessions a research staff member will walk the subject over to the MRN MRI scanning room. There the MRI technician will interact with the subject to safely complete the MRI scan.

Finally, for the two blood tests (baseline and 6 weeks visits) the subject and a family member or close friend will go to the Tricore Lab in the early AM (7-9AM) for the blood draw. If a relative/friend is not available to accompany the subject, a research staff member will meet the subject at the Tricore Lab.

22. Economic Burden to Subjects

22.1. Describe any costs that subjects may be responsible for because of participation in the research. Clearly stipulate what procedures are standard of care and what procedures are research-related in the table below. Please place an X in the box for the responsible party for each procedure involved.

List any costs to participants (or their 3rd party payer); include any charges for study procedures, visits, or drug/devices.

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
Clinical interviews	7	☒	☐
Blood tests	2 (1 for HVs)	☒	☐
MRI	2	☒	☐
Blinded study drug	6 weeks worth	☒	☐
Pregnancy tests	2	☒	☐
Urine drug screen	2	☒	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
medications for antipsychotic-induced extra-pyramidal side-effects (benztropine, propranolol, lorazepam)	3	☐	☒

medication for insomnia as needed (lorazepam , trazodone)	2	☐	☒
medication for claustrophobia as *needed* (lorazepam)	1	☐	☒

22.2. List any other costs to participants not already described above.

N/A

22.3. Indicate whether subjects will be charged for investigational drugs, devices, procedures

No

22.4. Explain who will be responsible for paying for treatment of adverse events

The subject and third party payers

22.5. Ensure that the cost section of the consent form reflects the cost that are covered by the sponsor and the costs for which the subjects (or 3rd party payers) are responsible.

Done

The costs of the MRIs, blinded medications, blood-work, urine drug-screens, pregnancy tests, and study visits required by the research will be covered by the study. FEP subjects (or their insurers) will be responsible for the costs of other drugs that may be prescribed like benztropine, lorazepam, propranolol, trazodone or other psychotropics that may be prescribed during the transition phase.

If incidental MRI findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

23. Compensation

23.1. Describe any plans for compensation or reimbursement for subjects (amounts, methods (e.g., merchandise card), and payment schedule; cash and checks are institutionally prohibited). Describe why the proposed amount is reasonable and appropriate for the subjects' time and inconvenience. Credit for payment should be prorated and not be contingent upon the participant completing the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn. Note: Consult with your department official for reporting requirements associated with cash or merchandise cards distributed to research subjects.

Participants will be compensated for their time and inconvenience. FEP participants could receive up to $310 for completion of the study. HV subjects can make up to $110. They will receive each payment via merchandise cards that will be given to subjects at the end of each visit. The cost of gas/transportation and the inconvenience of participating in this study, make these compensation rates fair and reasonable.

Baseline Visit (Clinical Interview) - $ 25
MR scan - $50 (x 2 for FEP, x 1 for HV)
Cognitive assessment - $25
Clinical ratings - $20 (x 7 for FEP)
Blood-work - $10 (x 2 for FEP; x 1 for HV)

24.Compensation for Research-Related Injury

24.1. If the research involves more than Minimal Risk to subjects, describe the plan for compensation in the event of research related injury.

24.2. If subjects are responsible for seeking their own form of care for research-related injury, describe how this will be communicated and what options are available to participants.

UNMHSC will provide subjects with emergency treatment, at their own cost. No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) or MRN to provide free medical care or money for injuries to participants in this study. In the event that the subject has an injury or illness that is caused by a subject's participation in this study, reimbursement for all related costs of care will be sought from their insurer, managed care plan, or other benefits program. If the subject does not have insurance, they may be responsible for the costs. Subjects will also be responsible for any associated co-payments or deductibles required by their insurance.

25.Consent Process

25.1. Indicate whether you will you be obtaining consent, and if so describe:

25.1.1. Who will be responsible for obtaining consent and their qualifications/training to do so. Be certain to identify which study team members will obtain consent in Huron under Project Contacts.

The research psychiatrists (Bustillo, Lenroot, and Dr Wylie) and the clinical research assistant (Garcia) will be obtaining consent. The psychiatrists have ample experience in research with this population. The research assistant Garcia has been trained by Drs Bustillo and Lenroot to interact with psychotic patients in a clinical research setting for the past 5 years. Dr. Tohen will not be obtaining consent due to his management plan by the HSC COI.

Participants will be initially screened over the phone or in person after they have expressed interest in the study. The participants will have initially been introduced to the study by a member of the research team or referring clinician. At the time of initial screening prior to consenting, if

the participant does not fit the inclusion criteria then the information that has been collected will be destroyed. Further screening procedures will occur in private office and trained study personnel will explain the nature and conditions of the study, review the elements of informed consent, and HIPAA, and administer signing of the consent statement and HIPAA. The Research assistants or investigators will additionally review the consent form page by page as trained, and at the end of each page ask the participant if they have any questions. Participants will be informed of the limits of confidentiality as a part of the consent process. If a participant has consented to be enrolled in the study they will sign and date the consent form and the consent form will also be signed by the research assistant or investigator. Research assistants will provide each participant with a copy of the HRPO-approved consent form. A urine screen for the presence of drugs may be administered, and a positive screen could result in an exclusion from study participation. If they have been enrolled in the study, and information has been collected then the information will be kept with a note as why the subject was a screen failed or reasons for withdrawing from the study.

Patients with psychotic disorders are not presumed to be incompetent to consent to treatment; these patients are not cognitively impaired like patients with dementia or delirium. Only in a minority of circumstances, like during involuntary hospitalization, they end up with an LAR who may give consent to treatment. Hence, in the 25 years our group has been doing research with subjects with psychotic disorders, we do not generally presume them to be unable to consent to participate in research. Most patients interested in participation will be experiencing delusional beliefs and/or hallucinations, but they will be fully alert, cooperative and oriented. Agitated psychotic patients are typically not interested in participation and will not be approached. Only subjects who can potentially remain in the MRI scanner still for 1 hour will be approached and this will effectively exclude potential subjects who have even mild agitation. A minority of psychotic subjects will have a significant amount of speech disorganization; these subjects are readily identified by our trained research staff who will discuss these characteristics with research psychiatrists Bustillo, Lenroot or Tohen for further evaluation. If the research psychiatrist confirms that speech disorganization impairs the subject's ability to consent, they will not be consented. Finally, some patients with psychotic disorders who were initially deemed unable to consent will improve with treatment and re-gain capacity to consent. If this occurs, and the subject suggests interest in participation, he/she may be approached for consent procedures. As stated above, these patients will not have their medications discontinued for the purpose of the study.

A waiver of written consent has been requested in order to contact family members/friends if the subject gives the research team permission to contact someone close to the subject. Minimal risk will be involved for family members/friends, and they will be read a script to inform them of the information that we will be gathering regarding the participant for research purposes. The majority of the information will be gathered by phone.

All participants will be fully informed as to the voluntary nature of the project, and they will receive a full explanation of the purpose of the study. Prospective participants will have multiple opportunities to ask questions. Participants will also be assured that they may withdraw from the study at any time even after agreeing to participate, so that if they experience discomfort during the procedures they may terminate participation or refuse to answer any particular item without penalty.

25.1.2. Where will the consent process take place and the provisions for privacy.

The consent process for outpatients and healthy volunteers will take place in a private room with the door closed at the Clinical Psychiatric Research Center (CPR). For patients hospitalized at UPC, the process will take place in a private room in the hospital.

25.1.3. The steps that will be taken to minimize the possibility of coercion or undue influence

Participants will be initially screened over the phone or in person after they have expressed interest in the study. The participants will have initially been introduced to the study by a member of the research team or referring clinician. At the time of initial screening prior to consenting, if the participant does not fit the inclusion criteria then the information that has been collected will be destroyed. After screening, the participant will be given a copy of the Consent Form for them to read it and ideally go over it with a loved one. In a different day from screening, in a private office (or by zoom if necessary) trained study personnel will further explain the nature and conditions of the study, review the elements of informed consent and HIPAA, and administer signing of the consent statement and HIPAA. The Research assistants or investigators will additionally review the consent form page by page as trained and at the end of each page ask the participant if they have any questions. Participants will be informed of the limits of confidentiality as a part of the consent process. If a participant has consented to be enrolled in the study they will sign and date the consent form and the consent form will also be signed by the research assistant or investigator as a witness. Research assistants will provide each participant with a copy of the IRB-approved consent form.

25.1.4. The waiting period available between reviewing the study and consent with the potential subject and obtaining the consent.

Waiting period will be at least one day.

25.1.5. Processes to ensure ongoing consent throughout the study.

For FEP participants, at the beginning of each follow-up visit, the psychiatrist will ask the subject if they have questions about the study procedures and whether they want to continue to participate. All participants will be fully informed as to the voluntary nature of the project, and they will receive a full explanation of the purpose of the study. Prospective participants will have multiple opportunities to ask questions. Participants will also be assured that they may withdraw from the study at any time even after agreeing to participate, so that if they experience discomfort during the procedures they may terminate participation or refuse to answer any particular item without penalty.

25.1.6. Any steps that will be taken to enhance understanding

Patients with psychotic disorders are not presumed to be incompetent to consent to treatment; these patients are not cognitively impaired like patients with dementia or delirium. Only in a minority of circumstances, like during involuntary hospitalization, they end up with an LAR who may give consent to treatment. Hence, in the 25 years our group has been doing research with subjects with psychotic disorders, we do not generally presume them to be unable to consent to participate in research. Most patients interested in participation will be experiencing delusional beliefs and/or hallucinations, but they will be fully alert, cooperative and oriented. Agitated psychotic patients are typically not interested in participation and will not be approached. Only subjects who can potentially remain in the MRI scanner still for 1 hour will be approached and this will effectively exclude potential subjects who have even mild agitation. A minority of psychotic subjects will have a significant amount of speech disorganization; these subjects are readily identified by our trained research staff who will discuss these characteristics with the research psychiatrists Bustillo, Lenroot or Tohen for further evaluation. If the research psychiatrist confirms that speech disorganization impairs the subject's ability to consent, they will not be consented. Finally, some patients with psychotic disorders who were initially deemed unable to consent will improve with treatment and re-gain capacity to consent. If this occurs, and the subject suggests interest in participation, he/she may be approached for consent procedures. As stated above, these patients will not have their medications discontinued for the purpose of the study.

25.1.7. Any procedure/testing for ensuring that the consent is understood by the potential subject (e.g., teach back)

After explanation of the study by staff the interested FEP subjects will complete a 10 question multiple choice quiz (Test for consent attachment) to ascertain their understanding of the study. They will not be able to sign the Consent Form until they pass the quiz (at least 8 out of 10 correct answers).

25.1.8. There are no provisions for a waiver of consent for FDA regulated research.

Subjects not fluent in English

Indicate what language(s) other than English are understood by prospective subjects or representatives.

Besides English, the only other primary language allowed for potential subjects will be Spanish. Drs Bustillo, Tohen and assistant Garcia are all fluent in Spanish.

25.1.9. If you anticipate enrolling subjects who do not understand or have limited fluency in English, describe the process to ensure that the oral and written information provided to those subjects initially and throughout their participation will be in the language they understand (e.g., use of translations and interpreters). Please note that translations of consent documents and subject materials will likely be required once the content of the English-language version is approved.

Non-english speakers will not be included.

25.1.10. Short-form consent documents are available for unanticipated enrollments of persons who don't understand or have limited fluency in English. However, based upon the nature of the research (e.g., clinical trials) subsequent translation of the consent document may be required so that the subject has access to written information about the research in a language they understand.

These requirements will be implemented.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.1.11. The HRRC must specifically approve the enrollment of adults unable to consent and adults with cognitive impairment or limited decision-making capacity. Complete the applicable checklist in the Checklists Section of this Protocol Template.

Most FEP subjects are not presumed to be unable to consent. See above 21.1.16 to see how this will be determined.

25.1.12. Describe whether the entire subject population or a portion of it is expected to have limited or no ability to provide legally effective consent.

Only a small portion is expected to be unable to consent as described in 21.1.16 . For these subjects an LAR would have to consent and the participant will have to assent.

25.1.13. Describe the process to determine whether an individual is capable of consent.

See above 21.1.16 and 21.1.17. Participants will be asked the questions in the Test for Consent attachment. Participants who receive 8 out of 10 or better will sign the consent. Further explanation will be provided to those who score less than 8 out of 10 until they obtain a passing score.

25.1.14. Describe the process to determine whether a prospective subject is capable of providing consent. Include who will be responsible for determining capacity and how it will be documented.

See above 21.1.16 and 21.1.17.

25.1.15. Describe how the participant's decisional capacity will be assessed as the study proceeds in order to evaluate any fluctuation in the participant's level of capacity to consent.

See above 21.1.15

25.1.16. If it can be anticipated that some or all subjects will regain capacity to provide consent, describe the provisions to provide them with information about their participation in the research and to seek their consent for ongoing participation, if applicable.

Some patients with psychotic disorders who were initially deemed unable to consent will improve with standard treatment and re-gain capacity to consent. If this occurs, and the subject suggests interest in participation, he/she may be approached for the consent procedures as described above.

25.1.17. For research conducted in New Mexico, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative."

An LAR must provide written legal documentation that confirms their appointment before allowed to consent for a FEP subject.

25.1.18. For research conducted outside of the New Mexico, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research.

N/A

25.1.19. Describe how the representative's authority to provide consent will be confirmed.

They must provide a copy of the appropriate document.

25.1.20. Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*

All subjects with an LAR will be asked to assent.

- *If assent will not be obtained from some or all subjects, an explanation of why not.*

N/A

- *Describe whether assent of the subjects will be documented and the process to document assent*

Yes.

Subjects who are not yet adults (infants, children, teenagers)

N/A

25.1.21. Provide the age range of the children anticipated to be enrolled in the research. N/A

25.1.22. Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted.

- *For research conducted in New Mexico, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*
- *For research conducted outside of New Mexico, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted.*

25.1.23. Describe whether parental permission will be obtained from:

- *One parent (may be permissible, if the HRRC approves, for (1) research not involving greater than minimal risk, or (2) research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects)*
- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (Permissible for research involving greater than minimal risk and no prospect of direct benefit to individual subjects.)*

25.1.24. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent.

25.1.25. Indicate whether the children to be enrolled in the research should be capable of providing assent.

25.1.26. Indicate if assent will be obtained from all, some, or none of the children and provide justification. If assent will be obtained from some children, indicate which children will be asked for assent.

25.1.27. When assent of children will be obtained describe the proposed assent process and whether and how assent will be documented. The assent process and documentation of assent should be age-appropriate and may consist of different procedures for different age groups.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

For all FEP and healthy volunteer subjects there will not be a waiver or alteration on the consent process.

In order to complete the Social Level of Functioning (SLOF) for FEP subjects, a relative, friend or clinician informant must be contacted. A waiver of written consent has been requested in order to contact family members/friends/clinician if the subject gives the research team permission to contact someone close to the subject. Minimal risk will be involved for family members/friends/clinician, and they will be read a script to inform them of the information that we will be gathering regarding the participant for research purposes. The majority of the information will be gathered by phone. A script will be attached to study record.

- *Complete the applicable checklists in the Checklists section of this Protocol Template if you are requesting a waiver or alteration of consent for this research*
- *Consent can be waived for all of some subjects (e.g., the research includes a retrospective cohort)*
- *Consent can be waived in full or in part (e.g., partial waiver for recruitment purposes)*

26.Documentation of Consent

26.1. Describe if you plan to use a consent form to document consent. Use one of the consent templates available on the HRPO website. Attach consent documents as fully editable Word documents (i.e., please don't submit protected documents or pdfs). Please include page numbers in the footer (e.g., Page 1 of XX).

Will use a Consent Form (attached).

26.2. If the study is collecting and/or storing tissue samples, include a Tissue Banking Consent Form (and Authorization if the specimens will be accompanied by PHI).

N/A

26.3. Describe if you plan to obtain consent but will be using a script, information sheet, or other mechanism. If you will obtain consent verbally, attach a consent script and information sheet, if you will be providing one. If you will be obtaining consent via an on-line survey, please use the survey cover letter consent template on the HRPO website and include your email script with your submission.

Complete the checklist for "Waiver of Documentation of Consent" in the Checklists section of this Protocol Template. If you will be excluding or modifying one or more of the required elements of consent you will also need to request an Alteration of Consent.

N/A

26.4. If FDA regulated, there is no provision for waiver of written documentation of consent.

27.Study Test Results/Incidental Findings

27.1. ***Individual Results:*** *Indicate whether you intend to share study test or procedure results with study participants. If so, describe which results will be shared, whom the results will be shared with (e.g., subjects, parents, primary care physicians), and how the findings will be communicated (e.g., in person consultation, posting in medical record, etc.). If the findings are the results of laboratory tests, indicate whether the tests will be processed in a CLIA-certified lab.*

Study test results (neuroimaging, cognitive, blood metabolic, and clinical measures) will not be shared with participants. A clinical reading of the MRI image by a neuro-radiologist will be shared with all subjects. Also, the baseline clinical blood work results will be shared with the FEP participant and with their LAR (if appropriate). All the clinical bloodwork (CBC, TSH, liver panel, Chem-7 and urinalysis, lipid panel, blood sugar, and prolactin) results will be posted in the patient's UNM hospitals electronic medical records. This is clinically useful information that will be made available for the patient's primary care and behavioral care providers to access. The results of the urine drug tests, urine pregnancy tests, and the research genetic tests will not be posted to the medical record.

27.2. ***Incidental Findings:*** *Based upon the nature of the research, and the tests that will be performed, indicate if you anticipate that the research may result in incidental findings (traditionally defined as results that arise that are outside the original purpose for which the test or procedure was conducted (for example, a potential tumor is identified but this is not the reason imaging was obtained). If so, please describe your plans for communication of such results to subjects and their health care providers, if appropriate. If there are limitations on the accepted validity of the results (e.g., test performed in non-CLIA lab, test available in the context of research only), please describe and provide a plan for confirmatory testing or justification for why it is not recommended, not necessary, or not possible. If you do not plan to provide results, provide justification.*

- *Be certain to describe your plans for provision of study results and incidental findings in your consent documents.*

- *For more information on incidental findings, please consult the President's Bioethics Commission Report "Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts": http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf*
- *For information specific to Whole Genome Sequencing, please consult the President's Bioethics Commission Report "Privacy and Progress in Whole Genome Sequencing": http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf*

All research MRI scans are read for incidental findings by a neuroradiologist unless the individual has been scanned at the Mind Research Network in the previous six months. If the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions.

Due to the very high sensitivity of MRI in detecting abnormalities, there is a risk of false-positive findings, identifying something on imaging studies that may or may not be important. This may result in anxiety and referral for additional medical testing, possibly including a recommendation for clinical scans at the participant's cost.

28.Sharing Study Progress or Results with Subjects

28.1. Describe whether you intend to provide subjects with a summary of the trial progress while the study remains underway. If so, describe your plans and the mechanisms that you will use (e.g., newsletter, handouts, mailings, etc.). Please note that all written materials that will be provided to subjects need to be reviewed and approved by the HRRC prior to use.

No summary of the trial progress will be provided to any subjects.

28.2. Describe whether you intend to provide subjects with a summary of the study results after the study is complete. If so, indicate if the information will include study arm assignment if the study involved blinding. Please describe your plans for dissemination of results and the mechanisms that you will use. Please note that HRRC review of materials may be required, consult with the HRPO prior to distribution.

The MRI scan is being done to answer research questions, not to examine the subject's brain for medical reasons. This MRI scan is not a substitute for a clinical scan (the type a doctor would order). All research MRI scans are read by a neuroradiologist unless the individual has been scanned in the previous six months (the second MRI scan in psychotic patients, will not be read by the neuro-radiologist). When the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the research psychiatrist/PI will also be notified and the participant will be contacted by phone to address any questions and get the right follow-up. The research team is always available to answer any questions they may have about the subject's scan.

29. Inclusion of Vulnerable Populations

29.1. If the research involves individuals who are vulnerable to coercion or undue influence, describe who will be included, why their participation is necessary or warranted, and any additional safeguards included to protect their rights and welfare. The following is not intended to serve as a comprehensive list, rather to provide some examples for your consideration.

29.1.1. If the research includes students or employees, describe protections to promote the voluntary nature of participation and minimize the risks associated with access to or use of data by persons in a position of actual or perceived authority. N/A

29.1.2. If the research includes economically disadvantaged persons, describe the mechanisms to promote the voluntary nature of participation and to minimize economic risks associated with participation. N/A

29.1.3. If the research includes educationally disadvantaged persons, describe the mechanisms to ensure that they are provided information and materials that enhance their ability to understand the research initially and throughout their participation in the research. N/A

29.1.4. If the research includes seriously or terminally ill patients, describe the mechanisms to ensure that they understand the true purposes of the research, the risk it entails, and what is known or not understood about the likelihood of individual benefit. N/A

29.1.5. If the research involves pregnant women, note this here and complete the Pregnant Women Checklist in the Checklist Section of this Protocol Template. N/A

29.1.6. If the research involves neonates of uncertain viability or non-viable neonates, note this here and complete the applicable checklist in the Checklist Section of this Protocol Template. N/A

Note: For the purposes of the federal research regulations, viability is established shortly after delivery. "Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration." Once a neonate has been determined viable, they are considered a child under the regulations.

29.1.7. If the research involves prisoners, note this here and complete the Prisoners Checklist in the Checklist Section of this Protocol Template. N/A

29.1.8. If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), note this here and complete the Children Checklist in the Checklist Section of this Protocol Template. N/A

29.1.9. If the research involves cognitively impaired adults, note this here and complete the Cognitively Impaired Adults Checklist in the Checklist Section of this Protocol Template.

The patient population will be recruited primarily on a clinician referral basis, thus subjects deemed at risk or too vulnerable will not be referred by their physicians. No vulnerable populations will be included in the study.

Legal Adult Representatives (LARs): Subjects that have court-appointed LARs will be accepted into the study. LARs will consent on behalf of the subject and the subject will verbally assent to study participation. LARs will sign the consent form at the designated LAR signature line.

30.Community-Based Participatory Research

30.1. Describe involvement of the community in the design and conduct of the research. If members of the community will fulfill key research responsibilities such as recruitment and consent, describe what research activities community members will be responsible for, how they will be trained, and the plan for quality oversight. When relevant, please include information regarding the approval of the research at collaborating sites (e.g., Albuquerque Public Schools).

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

N/A

31.Research Involving American Indian/Native Populations

31.1. Please provide detailed information of the local research context including how the research questions are sensitive to community attitudes and how the PI has ascertained that the proposed research is acceptable to the local population in terms of tribal regulations, applicable law and standards of professional conduct and practice. Attach any supporting documents from tribal officials or entities addressing the status or requirements for review of the research activity from tribal officials or tribal entities (for example, Indian Health Services, the Navajo Nation IRB).

N/A

32.Transnational Research

32.1. When conducting transnational research, you must ensure that subjects are provided equivalent and appropriate protections for human subjects located outside of the United States. Please refer to the following website for current OHRP interpretations of research standards, equivalent protections, and for a current compilation of international research standards and regulatory agencies. http://www.hhs.gov/ohrp/international/index.html

32.2. ***Location:*** *Describe the research locale and how and why the setting was chosen. Describe significant cultural norms, local laws, and differences with U.S. culture with respect to autonomy, perception of research, recruitment, consent, age of majority, parental permission, etc.*

32.3. ***Study Personnel:*** *Describe the qualifications of the researcher and research team to perform research in the community/culture where it will occur. Indicate the research team's ability to speak, read, and write the language of the subjects. Describe the researcher's knowledge of or expertise in local or state laws, culture, and community norms. Indicate if the researcher was invited into the community (provide documentation, if available). If not invited, then describe how the researcher will have culturally appropriate access to the community.*

32.4. ***Consent:*** *Describe the consenting procedure that you intend to use for the research and why it is appropriate for the community where the research will occur. Describe how you will ensure that potential subjects understand the research, and the voluntariness of their participation.*

32.5. ***Community Consultation:*** *Describe any plans for community consultation to assess receptiveness to the proposed research and to obtain feedback on how it should be conducted and any limitations or boundaries that should be respected. Describe plans for dissemination of results to subjects and to the community.*

N/A

33.Drugs or Devices

33.1. If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

33.2. If the drug is investigational (has an IND), identify the holder of the IND/IDE/Abbreviated IDE.

Both drugs are FDA approved for the treatment of psychotic disorders. An IND exemption has been approved by the FDA for the use of lumateperone in bipolar-I mania and mixed episodes with psychotic features, schizophreniform, schizoaffective, delusional, and unspecified schizophrenia spectrum and other psychotic disorders.

33.3. For research involving drugs, complete and attach a signed "Drug Attachment", available in Huron IRB or the HRPO website. Attached.

33.4. For research involving devices, complete the "Device Checklist" in the Checklist Section of this template.

N/A.

34.Principal Investigator's Assurance

By submitting this study in the Huron IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is to be directly entered onto a data collection form that is stored in a secured access folder on HSC central IT managed network storage (such as the N:\Research-Studies drive), or in a secure HSC Information Security approved system such as REDCap.
2. **Temporary storage -- de-identified data collection**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be temporarily stored using encrypted removable (e.g. CD-ROM (a compact disc used as a read-only optical memory device for a computer system), USB flash/thumb drive (a small external flash drive that can be used with any computer that has a USB port), etc.) media or a university owned electronic storage device or hard copy document. This temporarily stored data must be transferred to HSC central IT managed network storage and deleted from the temporary device as soon as possible. **The important security safeguard is that no identifiers be included if the data is entered or stored using a storage container that is not managed by HSC central IT.**
3. **Permanent (during data analysis, after study closure) storage** must reside on HSC central IT managed network storage (such as the N:\Research-Studies Drive). Processing of data (aggregation, etc.) are to be carried out in such a way

as to avoid creating/retaining files on untrusted or unsecure storage devices/computers (an example of an unapproved storage location would be storing the data locally on your HSC computer hard drive rather than on the HSC network drives). Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.

4. **Alternate storage media** must be approve by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

35.CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

36.Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

N/A

A. Describe the data source that you need to review (e.g., medical records):

B. Describe the purpose for the review (e.g., screening):

C. Describe who will conducting the reviews (e.g., investigators, research staff):

D. Do all persons who will be conducting the reviews already have permitted access to the data source?

☐ Yes

☐ No. Explain:

i. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

1. <u>The activity involves no more than minimal risk to the subjects</u> because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

☐True

☐Other justification:

2. <u>The waiver or alteration will not adversely affect the rights and welfare of the subjects</u> because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

☐ True

☐ Other justification:

3. The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

   ☐True

   ☐Other justification:

4. Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

   ☐True

   ☐Other justification:

37.Partial Waiver of HIPAA Authorization for Screening/Recruitment

Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

N/A

A. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☐ No

B. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

C. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

38.Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

N/A

A. Are you requesting a waiver of documentation of consent for some or all subjects?

☐All

☐Some. Explain:

B. Provide justification for <u>one</u> of the following:

i. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

ii. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

C. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

☐Yes. Please attach a copy to your submission in Huron IRB.

☐No

39.Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

N/A

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

A. Which element(s) of consent do you wish to eliminate <u>and</u> why?

B. Which element(s) of consent do you wish to alter and why?

C. Provide justification for each of the following regulatory criteria:

i. The research involves no more than minimal risk to the subjects:

ii. The waiver or alteration will not adversely affect the rights and welfare of the subjects:

iii. The research could not practicably be carried out without the waiver or alteration:

iv. Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

40. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

N/A

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

A. Are you requesting a waiver for some or all subjects?

☐All

☐Some. Explain:

B. Provide justification for each of the following regulatory criteria:

i. The research involves no more than minimal risk to the subjects:

ii. The waiver or alteration will not adversely affect the rights and welfare of the subjects:

iii. The research could not practicably be carried out without the waiver or alteration:

iv. Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

N/A

A. Are you requesting a waiver for some or all subjects?

☐All

☐Some. Explain:

B. Provide justification for each of the following regulatory criteria:

i. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

ii. The research could not practicably be carried out without the waiver or alteration.

42. Full Waiver of HIPAA Authorization (Checklist)

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort).

Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

N/A

A. Are you requesting a waiver of authorization for some or all subjects?

☐All

☐Some. Explain:

B. Describe your plan to protect health information identifiers from improper use and disclosure:

C. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

D. Describe why the research could not practicably be conducted without the waiver or alteration:

E. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

☐True

☐False

43.Other Waiver Types (Checklist)

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

44.Vulnerable Populations (Checklist)

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

Patients with psychotic disorders are not presumed to be incompetent to consent to treatment; these patients are not cognitively impaired like patients with dementia or delirium. Only in a minority of circumstances, like during involuntary hospitalization, they end up with an LAR who may give consent to treatment. Hence, in the 25 years our group has been doing research with subjects with psychotic disorders, we do not generally presume them to be unable to consent to participate in research. Most patients interested in participation will be experiencing delusional beliefs and/or hallucinations, but they will be fully alert, cooperative and oriented. Agitated psychotic patients are typically not interested in participation and will not be approached. A minority of psychotic subjects will have a significant amount of speech disorganization; these subjects are readily identified by our trained research staff who will discuss these characteristics with research psychiatrists for further evaluation. If the research psychiatrist confirms that speech disorganization impairs the subject's ability to consent, they will not be consented.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

   Some patients with psychosis will have disorganization of thinking and cognitive impairment. These are usually the sickest patients. Hence excluding them because they cannot consent would result in a sample that is not representative of the broad psychopathology of psychotic disorders. Therefore, as in many of our previous neuroimaging and pharmacological studies in this population, we propose to include these sicker patients but only if an LAR has been appointed. Still these patients would have to additionally assent in order to be considered for the study.

2. Describe how capacity to consent will be evaluated.

   Evaluated by research psychiatrists for speech disorganization. If speech disorganization impairs subject's ability to consent they will not be consented unless they have an LAR who is able to consent on their behalf. Additionally, every subject (or LAR) will complete the 10 question test (attached) to document comprehension of study protocol.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

Some patients with psychotic disorders who were initially deemed unable to consent will improve with treatment and re-gain capacity to consent. If this occurs, and the subject suggests interest in participation, he/she may be approached for consent procedures. Unlike subjects with delirium, psychotic subjects will not have fluctuating capacity to consent.

Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

Participants will be initially screened over the phone or in person after they have expressed interest in the study. The participants will have initially been introduced to the study by a member of the research team or referring clinician. Further screening procedures will occur in private office and trained study personnel will explain the nature and conditions of the study, review the elements of informed consent, and HIPAA, and administer signing of the consent statement and HIPAA. The Research assistants or investigators will additionally review the consent form page by page as trained, and at the end of each page ask the participant if they have any questions. After explanation of the study by staff the interested FEP subjects will complete a 10 question multiple choice quiz (Test for consent attachment) to ascertain their understanding of the study. They will not be able to sign the Consent Form until they pass the quiz (at least 8 out of 10 correct answers). If a participant has consented to be enrolled in the study they will sign and date the consent form and the consent form will also be signed by the research assistant or investigator. Research assistants will provide each participant with a copy of the HRPO-approved consent form.

4. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

   Based on our 25 year experience with this clinical population, we expect a minority of FEP subjects will have an assigned LAR. If they do and the referring clinician believes that the patient may meet study inclusion criteria, the LAR will be approached by study staff. If LAR consents to the study, the FEP subject will be asked to assent to the study by signing the appropriate assent line in the consent form. If FEP subject declines to assent, he/she will not be included in the study.

5. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

FEP subjects will have the following risks: 1- Side-effects of either one from two standard antipsychotic medications; the standard of care for these subjects is treatment with an antipsychotic medication for weeks or months; 2- risk of worsening of symptoms because they happen not to respond to the assigned medication; 3-risk of MRI, a non-invasive neuroimaging test; 4- risk from blood draw; risk of stress/fatigue form clinical/cognitive assessments; and 5- risk to confidentiality. The potential benefits are minimal because subjects can have access to both medications and an MRI of the brain through their regular

provider. However, the risks are considered reasonable because they differ minimally (2 MRI's, 2 blood draws, longer and more frequent clinical assessments) from the risks that are part of the standard of care for patients in their first episode of psychosis that require treatment.

6. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

The study does involve a health intervention: the treatment with an antipsychotic, either risperidone or lumateperone; their anticipated benefit (improvement of psychosis) to risks (extrapyramidal side-effects and metabolic side-effects), are the same as with alternative procedures (aripiprazole, quetiapine, ziprasidone, etc).

7. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

FEP subjects will be seen by a research psychiatrist every week to monitor response to study medicine and tolerability. This is more frequent than the standard of care (visits every few weeks). Medication dose will be adjusted weekly as clinically indicated. If extrapyramidal side-effects are present, the study medication dose may be reduced or benztropine, propranolol or lorazepam may be prescribed as clinically indicated. The patient will be counselled weekly to prevent metabolic side-effects, like weight gain. Alternatively, the assigned study medication can be switched to the alternative blinded medication for lack of efficacy or intolerance as per protocol. If the subjects distress is severe or persistent they may be withdrawn from the study at any time and the research psychiatrist will ensure the subject is referred for appropriate local psychiatric care.

B. Children

Complete this checklist if the subject population will include children.

N/A

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

☐Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those*

ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)

☐Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

N/A

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, EPA, or VA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates

Complete this checklist if the subject population will include neonates of uncertain viability.

N/A

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates

Complete this checklist if the subject population will include nonviable neonates.

N/A

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

   ☐True

   ☐False

6. The research will not terminate the heartbeat or respiration of the neonate

   ☐True

   ☐False

7. There will be no added risk to the neonate resulting from the research

   ☐True

   ☐False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

N/A

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

   ☐Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

   ☐Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

   ☐Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

   ☐Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

   ☐Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

   a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

b) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers

c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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45.Medical Devices (Checklist)

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

N/A

A. Device Name:

B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?

☐Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☐No

D. Is the research IDE-exempt?

☐Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☐No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

46.Export Control (Checklist)

Indicate if there will be export control concerns (i.e., select agents or select toxins involved in the project, collaboration with foreign institution or foreign nationals, publication restrictions, foreign travel, etc.). If so, please upload and complete Export Control Exclusion Screening Form


EC-Screening-Form-FILLABLE 12-1-14.pd

N/A.

47. Data Transfer/Sharing/Storage (Checklist) (required –do not delete even if the answer is "No")

N/A

Data Use Agreement (DUA) Contacts:

Sponsored Projects Office

- Aida Andujo, Manager, AAndujo@salud.unm.edu
- Siiri Wilson, Contract Specialist, SiWilson@salud.unm.edu

Privacy Office

- Laura Putz, Privacy Officer, LPutz@salud.unm.edu
- Gayle Shipp, Privacy Specialist, GShipp@salud.unm.edu

Information Security Office

- Information Security Office, HSC-ISO@salud.unm.edu

Provide all information requested if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will UNM data be transferred/shared with an external entity (i.e. another institution, company, etc.) or will an external entity's data be transferred/shared with UNM?

☐Yes. **If yes, all questions must be answered congruently based on protocol provisions.**

☒ No. **If no, the remainder of this section does not apply.**

B. Indicate if the data is incoming, outgoing or both:
C. Provide the name of the entity(s) that data will be transferred/shared with, if incoming:

D. Provide the name of the entity(s) that data will be transferred/shared with, if outgoing:

E. Provide the external entity(s) contact name, email and phone number with whom the data agreement is going to be executed. List contact information for each external entity(s) that are involved with the project.

Contact Name	External Entity	Email	Phone Number

F. Who is responsible for transmission of the data (include name, email address and phone number)?
G. Who is responsible for receiving the data (include name, email address and phone number)?

H. Describe how the data will be securely transmitted/shared . Please note data cannot be transmitted/shared without assistance from UNM HSC Central IT. **RequestHSC Central IT Transfer from the ISO office. (cannot transfer via email, cloud storage services such as Dropbox OneDrive, and fax)**

I. For data being transferred/shared with outside locations or entities, describe the following:

1. Where will data be stored and how will it be protected? (i.e. encryption, password protection, access controls, use ofREDCap, etc)?
   - *If REDCap, who manages/owns REDCap (i.e. UNM HSC or other external entity)?*
   - *If REDCap or other external system is not UNM HSC REDCap managed/owned, please provide the name and contact information of owner and the access (login) link?*

     Provide IT security point of contact details for externally managed/owned REDCap:
2. What is the method being used for data collection and storage (i.e. electronic, hard copy, etc.)?
3. How long will the data be stored? Must be congruent with sections 16.16-16.18.
4. Where will data be stored? (UNM HSC requires that research data be stored on the N:\Research-Studies drive managed by HSC Central IT.)
5. Who will have access to data?

J. Please list all specific data elements, variables, etc. to be sent out (outgoing) and/or received (incoming).
What data is incoming?
What data is outgoing?

K. What is the classification of the data (de-identified, limited data set, protected health information, other)? See below for definitions:
DE-IDENTIFIED DATA: Identifiers That Must Be Removed to Make Health Information De-Identified:
(i) The following 18 identifiers must be removed of the individual or of relatives, employers or household members of the individual must be removed: (A) Names; (B) All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.(C) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; ***and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;*** (D) Telephone numbers; (E) Fax numbers; (F) Electronic mail addresses; (G) Social security numbers; (H) Medical record numbers; (I) Health plan beneficiary numbers; (J) Account numbers; (K) Certificate/license numbers;(L) Vehicle identifiers and serial numbers,

including license plate numbers; (M) Device identifiers and serial numbers; (N) Web Universal Resource Locators (URLs); (O) Internet Protocol (IP) address numbers; (P) Biometric identifiers, including finger and voice prints; (Q) Full face photographic images and any comparable images; and (R) Any other unique identifying number, characteristic, or code; and (ii) The covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information.

LIMITED DATA SET: A "limited data set" is a limited set of identifiable patient information as defined in the Privacy Regulations issued under the Health Insurance Portability and Accountability Act (HIPAA). A "limited data set" is information from which "facial" identifiers have been removed. A "limited data set" is information from which "facial" identifiers have been removed. Specifically, as it relates to the individual or his or her relatives, employers or household members, all the following identifiers must be removed in order for health information to be a "limited data set": names; street addresses (other than town, city, state and zip code); telephone numbers; fax numbers; e-mail addresses; Social Security numbers; medical records numbers; health plan beneficiary numbers; account numbers; certificate license numbers; vehicle identifiers and serial numbers, including license plates; device identifiers and serial numbers; URLs; IP address numbers; biometric identifiers (including finger and voice prints); and full face photos (or comparable images).

The health information that may remain in the information disclosed includes: dates such as admission, discharge, service, DOB, DOD;
city, state, five digit or more zip code; and
ages in years, months or days or hours.

It is important to note that this information is still protected health information or "PHI" under HIPAA. As a limited data set the information is still subject to the requirements of the federal and state privacy and security regulations.

PROTECTED HEALTH INFORMATION (PHI): PHI is defined as any individually identifiable health information collected or created as a consequence of the provision of health care by a covered entity, in any form, including verbal communications. PHI is information that can be linked to a particular person and that is created, used, or disclosed in the course of providing a health care service (i.e., diagnosis or treatment). There are 18 PHI identifiers as listed in the de-identified data definition section.

L. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify, contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information? ☐Yes ☐No

   If yes, please provide details regarding the consent process:

   a. ***Or*** is HIPAA authorization altered or waived? ☐Yes☐No

   If yes, please provide details:

M. Does the request to transfer/share data include clinical data that belongs to the UNM Health System? If data originates from the UNM Health System medical records, this question should be answered "Yes". ☐Yes ☐No

N. Does the data to be transferred/shared include information about patients seen at an external health system or at a third party medical provider? ☐Yes ☐No
If yes, please provide details:

O. Is the external entity a "covered entity"? (HIPAA-covered entities include health care providers (i.e. hospitals, doctors, academic health centers), health plans, and clearinghouses.): ☐Yes ☐No

P. Is the data that is going to be transferred/shared owned or partially owned by another party? ☐Yes ☐No
If yes, please provide details:

Q. Does the data have any restrictions other than HIPAA? ☐Yes ☐No
If yes, please provide details:

R. Is the data publicly available? ☐Yes ☐No
If yes, please provide details:

S. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health? ☐Yes ☐No
If yes, please provide details:

48. Specimen Transfer/Sharing (Checklist) (required –do not delete even if the answer is "No")

Provide all requested information if the research involves transferring/sharing of specimens with an external entity (institution, company, etc.).

A. Will specimens be transferred/shared with an external entity (institution, company, etc.)?

☒ Yes. **If yes, all questions must be answered congruently based on protocol provisions.**

☐No. **If no, the remainder of this section does not apply.**

B. Indicate if the specimens are incoming and/or outgoing: *Incoming.*

C. Provide the name of the entity that specimens will be being transferred/shared with: Tricore.

D. Provide the contact name, email and phone number with whom specimens are being transferred/shared with: Michael Donelly

E. Who is responsible for sending out the specimens? Please note specimens cannot be sent out without a fully executed material transfer agreement. *Michael Donelly*

F. Who is responsible for receipt of the specimens? Please note specimens cannot be received without a fully executed material transfer agreement.

Will Wylie (psychiatry resident participating in research). He will take the samples to neuroscience for storage.

G. For specimens being transferred/shared with outside locations or entities, describe the following:

1. *Where is specimen storage and how will it be maintained in a secure manner? Freezer will be in a locked office.*
2. *What is method in which specimens will be collected and stored? Collected in PAXgene tubes and stored in -80C freezer.*
3. *How long will the specimens be stored? 3 years*
4. *Who will have access to the specimens? Dr. Bustillo, Dr. Wylie*

Materials will not be transferred until the MTA is fully executed. The fully executed and signed MTA will be uploaded to the study record once approved.