Cover Page - AMP SCZ® Observational Study

Accelerating Medicines Partnership® Schizophrenia Observational Study

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Content:

Study Protocol for Psychosis-Risk Outcomes Network (ProNET).

Northwell Health

RESEARCH PROTOCOL

Protocol Title:	ProNET
Principal Investigator:	John Kane
Primary Contact Name:	Patricia Marcy
Primary Contact Phone:	347-439-8035
Primary Contact E-mail:	pmarcy@northwell.edu
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Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
  - Your study is a registry or repository for data and/or samples, in this case, use *Protocol Template – Registry Studies.*
- If a section of this protocol is not applicable, please indicate such.
- Do not delete any of the text contained within this document.
- Please make sure to keep an electronic copy of this document. You will need to use it, if you make modifications in the future.
- Start by entering study information into the table above, according to these rules:
  - Protocol Title: Include the full protocol title as listed on the application.
  - Investigator: include the principal investigator's name as listed on the application form
  - Date Revised: Indicate the date at which the protocol was last revised
  - IRB Number: Indicate the assigned IRB number, when known. At initial submission, this row will be left blank.
- Once the table information in entered, proceed to page 2 and complete the rest of the form.

□ Continue to next page to begin entering information about this study □

1. PREVIOUS STUDY HISTORY

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

X No ☒ Yes − if yes, please explain: this is under umbrella protocol #

2. BRIEF SUMMARY OF RESEARCH

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

It has now been two decades since the clinical high risk for psychosis (CHR) criteria were first formulated in service of the goal of preventing psychotic disorders, one of the most urgent unmet clinical needs in behavioral health if not in all of medicine. As with most psychiatric patients, CHR patients benefit from psychotherapies but are also often left with important treatment needs not fully addressed. Despite the critical public health need, drug development for CHR is viewed in many quarters as risky. The most daunting obstacle may be the heterogeneity of CHR course. The goal of the ProNET study is to phenotype 1040 CHR participants and 390 healthy controls across the ProNET network of 26 international sites with multi-modal biomarkers, psychopathology and cognition, genetics, body fluid analytes, natural speech/language, and passive/ecological momentary digital phenotyping, and map these biomarkers onto a core set of clinical outcome measures and trajectories over 24 months. The hypothesis is that data-driven variation assessed by multivariate neural, genetic, and behavioral measures within the CHR syndrome predicts individualized clinical trajectories, expanding CHR stratification for broad clinical endpoints encompassing affect, anxiety, cognition, and APS with the goal of identifying behavioral and biomarker-driven patterns that can refine the CHR syndrome and promote personalized treatment decisions. These analyses will yield expanded outcome stratification calculators for the CHR syndrome that can predict actionable mental health trajectories in individual patients. The stratification calculators will allow future clinical trial designers to select optimal samples for determining whether a novel compound improves the particular CHR outcome of interest and pave the way for phase-specific and safe new interventions to benefit patients and their families and communities.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*

- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

Accelerating Medicines Partnership in Schizophrenia (AMP SCZ), a US-based public-private program with the overall aim of generating tools that will improve success in developing early stage interventions for patients who are at risk of developing schizophrenia and other psychotic disorders. The AMP SCZ current partners include government partners (NIH, FDA, European Medicines Agency), industry partners (Boehringer Ingelheim, Janssen, Otsuka), and non-profit partners (American Psychiatric Association Foundation, National Alliance on Mental Illness, One Mind, Schizophrenia and Psychosis Action Alliance, Wellcome).

Detection and intervention before psychosis develops, when individuals are at clinical high risk for psychosis, could attenuate, postpone, or even prevent the conversion to psychosis and improve individuals' clinical and functional outcomes. AMP SCZ aims to develop measures that further define early stages of risk and predict the likelihood of progression to psychosis and other clinical outcomes. Such tools will enable clinical trials to test new pharmacological interventions that may prevent or delay the onset of psychosis.

AMP SCZ partners will work towards the shared mission of discovering promising biological markers that can help identify those at risk of developing schizophrenia as early as possible, track the progression of symptoms and other clinical outcomes, including anxiety, depression, and substance use disorders, and define targets for treatment development.

NIMH funded two international networks to collect multimodal data in large samples of CHR participants: Psychosis-Risk Outcomes Network (ProNET) summarized in the following pages and PRESCIENT, led by researchers based at Orygen. Additionally, a Data Processing, Analysis, and Coordinating Center (DPACC, Harvard University) was funded with the purpose of integrating and analyzing data from new and key existing clinical high-risk cohorts, including the AMP SCZ cohort.

The clinical high risk (CHR) syndrome for psychosis spectrum disorders provides a key opportunity to prevent disease onset or ameliorate its course. Information emerging in the last decade from genetics and neurobiology is providing the first robust insights into disease mechanisms and therefore hope for interventions that can alter the course of these serious mental disorders. Yet, to safely intervene in pathogenic mechanisms during a period of significant brain development in still relatively healthy youth requires high confidence in prognostic and predictive biomarkers that can stratify individuals with this heterogeneous syndrome [1] into likely clinical trajectories and outcomes and match them with effective treatments. The goal of identifying and validating such biomarkers has motivated major international consortia (NAPLS, PRONIA, PSYSCAN, PNC) to study the CHR syndrome and map its underlying neural features. These efforts were recently unified via HARMONY, a consortium to inform quantitative biomarkers for mapping CHR psychosis trajectories. Despite major progress, these studies have also revealed a clear need for better powered, internationally coordinated efforts to prospectively standardize biomarkers that can inform interventional studies via state-of-the-art behavioral, neurobiological, and genetic measures. Such an effort should be designed to address key existing knowledge gaps: First, current CHR

definitions do not predict psychosis trajectories with adequate precision to yield clinically actionable stratification for outcomes. Only about 20% of patients progress to overt psychotic illness within two years of ascertainment [2]. While this percentage is far greater than chance, it falls far short of what it will take to initiate clinical trials of potential disease course altering interventions as they become available. Second, a substantial fraction of CHR patients who do not convert to frank psychosis continue to suffer persistent attenuated psychotic symptoms (APS), affective symptoms, cognitive deficits, and/or major functional impairments. Therefore, it is vital to deconstruct the heterogeneity of this syndrome and broaden CHR endpoints to quantify and predict individual clinical trajectories across the range of clinically relevant outcomes. Third, clinical trials for CHR have historically been linked to syndrome endpoints (i.e. conversion to psychosis or schizophrenia) that fail to capture outcome heterogeneity and limit therapeutic options. Finally, despite mounting evidence emerging from genetics, only limited efforts have been made to formally link neurobiological and genetic variables to each other and to the broader range of relevant CHR outcomes.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

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

The **P**sychosis-**R**isk **O**utcomes **N**etwork (**ProNET**) study proposes a standardized large-scale international effort to deconstruct CHR heterogeneity with state-of-the-art multimodal methods and map clinically relevant trajectories and outcomes of the CHR syndrome. ProNET will collect and quantify multi-modal prognostic or predictive biomarkers that span psychopathology and cognition, MR-based imaging, electrophysiology (EEG), genetics, fluid-based analytes, natural speech/language data, and digital phenotyping and passive/ecological momentary assessments. The end-goal of the effort is to develop a suite of predictive biomarkers that inform personalized treatment decisions and enable future clinical trials. To achieve this, we propose to:

Aim 1. Ascertain 1040 CHR individuals along with 390 healthy controls and collect multi-modal biomarkers that span brain structure-function (MRI and EEG), psychopathology and cognition, genetics, body fluid analytes, natural speech/language, and passive/ecological momentary digital phenotyping across 26 international sites and map these biomarkers onto clinical outcomes. Healthy controls support the interpretability of findings relating to the development of stratification tools within the CHR sample.

Aim 2. Partner with the NIMH-selected Data Processing Analysis and Coordinating Center at Harvard/Brigham and Women's for rapid data integration and NIMH Data Archive (NDA) uploads.

Aim 3. Test the hypothesis that data-driven variation assessed by multivariate neural, genetic, and behavioral measures within the CHR syndrome predicts individualized clinical trajectories, expanding CHR stratification for an array of clinical endpoints encompassing affect, anxiety, cognition, and APS. Aim 3 will unify information collected via Aims 1 & 2 to develop new technical capability for informing stratified/personalized CHR trajectories both for and beyond psychosis. The goal is to identify behavioral and biomarker-driven patterns (including several exploratory novel CNS biomarkers) that can refine the CHR syndrome with the ultimate goal of developing new pharmaceutical

treatments for personalized treatment decisions. The success of ProNET Aim 3, will yield expanded outcome stratification calculators for the CHR syndrome that can predict actionable mental health trajectories in individual patients.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

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

Each CHR site involved in the protocol will employ a part-time research coordinator/recruiter who will recruit participants into the study. This dedicated research coordinator/recruiter will be trained by the central team on all required research procedures. The central team has previous experience in the training and oversight of site research coordinators/recruiters. By employing a dedicated resource, the sites should have sufficient time to engage all eligible CHR participants allowing us to meet our enrollment goals. Sites will have the option of having CHR staff other than the research assistant participate in the consent process. These staff will also receive training by the central team on consent procedures.

6. RECRUITMENT METHODS

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

ProNET will recruit 1040 CHR participants and 390 healthy controls from the proposed network of 26 sites: including 17 in the US, two in Canada, five in Europe and two in Asia. All proposed sites have existing CHR research clinics with well-established referral sources. The proposed sites have an average recruitment rate of approximately 34 CHR participants per site over the last year. Almost all the participating sites have a long history of previous experience conducting CHR research studies and/or participating in a CHR network and/or CHR research study.

Each proposed site is well connected within their community and employs various activities to engage their referral network. Activities seen among many of the proposed sites may include but are not limited to:

• Dedicated CHR referral/intake coordinators to assist new referrals from initial contact to evaluation and enrollment

• Dedicated community outreach coordinator

• Presentations to community agencies, college counseling centers, high schools, emergency services, and youth agencies

• Outreach to community agencies utilizing brochures, flyers, quarterly newsletters, local websites, and social media

• Patient engagement programs

• Connecting with other health care providers in the community such as local health systems and hospitals, community mental health clinics, and private practitioners

• Individual meetings with other mental health providers in the community

• Participating in community health events such as mental health fairs

• Localized advertisement (program websites, social media, radio and newspaper ads)

In addition, ProNET will recruit a total of 390 demographically comparable healthy controls; all sites also have considerable experience recruiting adolescent and young adult typically developing control participants.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*
- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

CHR PARTICIPANTS

Inclusion criteria:

(1) Individuals between 12 and 30 years old;

(2) Understand and sign an informed consent (or assent for minors) document;

(3) Meet diagnostic criteria for CHR from the Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS).

Exclusion criteria:

(1) Antipsychotic medication exposure equivalent to a total lifetime haloperidol dose of >50 mg (see Table 1.0 for haloperidol equivalents), estimated based on available information (e.g., medical file documentation, participants and family report) or current antipsychotic medication at time of screening assessment;

(2) Documented history of intellectual disability;

(3) Past or current clinically relevant central nervous system disorder. When necessary, Research Assistants will consult with study team investigators (including medical personnel) to determine if the central nervous system disorder is deemed to be clinically relevant;

(4) Traumatic brain injury that is rated as 7 or above on the Traumatic Brain Injury screening instrument;

(5) Current or past treated or untreated psychotic episode, as determined using the PSYCHS.

HEALTHY CONTROL PARTICIPANTS

Inclusion criteria:

(1) Individuals between 12 and 30 years old;

(2) Understand and sign an informed consent (or assent for minors) document.

Exclusion criteria:

(1) Antipsychotic medication exposure equivalent to a total lifetime haloperidol dose of >50 mg (see Table 1.0 for haloperidol equivalents), estimated based on available information (e.g., medical file documentation, participants and family report);

(2) Documented intellectual disability;

(3) Past or current clinically relevant central nervous system disorder. When necessary, Research Assistants will consult with study team investigators (including medical personnel) to determine if the central nervous system disorder is deemed to be clinically significant;

(4) Traumatic brain injury that is rated as 7 or above on the Traumatic Brain Injury screening instrument;

(5) Meet criteria for any CHR psychosis-risk-syndrome, any current or past psychotic disorder or Cluster A personality disorder diagnosis;

(6) Must not be receiving any current treatment with psychotropic medication;

(7) Must not have a family history (in first-degree relatives) of psychotic spectrum disorders.

Table 1.0 ANTIPSYCHOTIC DOSE EQUIVALENTS
The doses provided in the table below are currently equivalent to a haloperidol dose of 50 mg. Please note that these may change over the course of the study. The RA must seek out the latest dose equivalent at the time of entry into the study for each participant this relates to.

Abbreviated Drug Name, Drug Name and Trade name		Dose in mg
AMS	Amisulpiride (Solian)	1875
APP	Aripiprazole (Abilitat, Abilify)	187.5
ASP	Asenapine (Saphris)	125
BRX	Brexpiprazole (Rexulti)	25
CRP	Cariprazine (Vraylar)	18.75
CPZ	Chlorpromazine (Largactil)	2500
CLZ	Clozapine (Clozaril)	2500
DPL	Droperidol (Droleptan)	100
FLH	Fluphenazine HCL (Anatensol)	50
HPL	Haloperidol (Haldol)	50
ILO	Iloperidone (Fanapt)	100

	LUM	Lumateperone (Caplyta)	525
	LUR	Lurasidone (Latuda)	1500
	OLZ	Olanzapine (Zyprexa)	125
	PAL	Paliperidone (Invega)	50
	PCZ	Pericyazine (Neulactil)	250
	PIM	Pimozide (Orap)	50
	PPH	Perphenazine (Trilafon)	200
	QTP	Quetiapine Fumarate (Seroquel)	1875
	RIS/RSP	Risperidone (Risperdal)	50
	SUL	Sulpiride (Dolmatil, Sulpitil, Sulparex)	5000
	THI	Thiothixene (Navane)	100
	THZ	Thioridazine (Mellaril, Aldazine)	2500
	TPZ	Trifluoperazine (Stelazine)	125
	ZPD	Ziprasidone (Geodon)	1500

8. NUMBER OF SUBJECTS

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

The ProNET study will enroll a total of 1040 CHR participants and 390 healthy control participants across 26 international sites. On average sites will enroll 2 new participants into their CHR program per month for a total of 40 participants per site recruited over approximately 24 months. Each site will recruit 15 healthy control participants that HC will be matched with CHR participants at each site across age, gender, parental socioeconomic status and parental education.

9. STUDY TIMELINES

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

Participants enrolled in ProNET will participate in outcome assessments over a two year period. Recruitment is expected to begin June 2022 and end in approximately May 2024. The last participant enrolled into the program will complete their final assessment by May 2026.

10. ENDPOINTS

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

In most research studies, the primary study endpoint is a defined outcome (e.g. a response or relapse criterion). For the ProNET the study endpoints differ in that success is measured by the ability to enroll and collect clinical and biomarker assessments from CHR participants. The data collected will help increase the understanding of the heterogeneity of CHR and assist in the development of tools for outcome definition and patient stratification.

11. RESEARCH PROCEDURES

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

ProNET will quantify behavioral outcomes and trajectories over a treatment-relevant time window at nine visits over 24 months. Biomarkers will be collected at two time points (baseline and month 2) to map brain-behavior trajectories and facilitate development and validation of empirically-grounded tools for patient segmentation in future clinical trials. Additionally, healthy controls (N=390) will complete screening, baseline, month 12, and month 24 assessment to quantify typical variation and of those 390 healthy controls N=130 healthy controls will be asked to also complete the month 2 visit.

All CHR participants will complete the assessments as listed in Table 2.0 ProNET CHR Schedule of Assessments below. Healthy Control participants will complete the assessments listed in Table 3.0 ProNET Healthy Control Schedule of Assessments.

1. **Screening Visit (week -3 to -1**) will take approximately 2-3 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments and Table 3.0 ProNET Healthy Control Schedule of Assessments
    a. **Informed consent:** All participants will have the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation explained to them and any questions will be answered. If a participant consents to participation in this study, the participant will review and sign the informed consent form (ICF). After both the participant and the investigator sign the ICF, each participant will be given a copy of the signed ICF.
    b. **Medical History:** Medical history, surgical history, and current medical conditions will be recorded. All relevant medical and surgical history within 10 years must be noted in the CRF. If a participant indicates a past traumatic brain injury, the Traumatic Brain Injury screening instrument will be completed.

c. **Schizotypal Personality:** The SCID-5 PQ is a semi-structured interview for DSM-5 and will be used to assess diagnostic criteria for Schizotypal Personality Disorder.
d. **Family History:** The Brief Family Interview for Genetic Studies (FIGS) will be administered to assess first-degree family history of psychosis and other major psychopathology domains
e. **Clinical High Risk (CHR) eligibility:** The Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS); will be administered to determine presence and severity of Attenuated Psychotic Symptoms (APS) and eligibility for the study. The participant can be included in the study if they meet criteria on the PSYCHS. Each item includes a number of sub-items which will be rated separately, with the highest rated sub-item constituting the rating for the respective item. With the consent of the participant, the PSYCHS portion of the visit will be voice and/or video recorded. These recordings will assist with ratings and quality assurance. They will also be transcribed and incorporated into the speech and facial expression analyses.
f. **The Social and Occupational Functioning Scale (SOFAS):** The SOFAS will rate an individual's level of social and occupational functioning.
g. **Past/Current Medications, Psychosocial Treatment, and Adverse Events:** Data will be collected from participants and parents on antipsychotic medication use supplemented by pharmacy and medical records as available.

2. **Baseline Visit: (month 0**) will take approximately 8-9 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments and Table 3.0 ProNET Healthy Control Schedule of Assessments. The baseline assessment is expected to be completed over 2-3 days within the same week.
    a. **Demographics:** Participant demographic information will include date of birth, sex, and race/ethnicity.
    b. **Positive Symptoms:** Positive symptoms will be assessed using the PSYCHS.
    c. **The Social and Occupational Functioning Scale (SOFAS):** The SOFAS will rate an individual's level of social and occupational functioning.

    d. **The Perceived Discrimination Scale**: Perceived discrimination will be assessed using an adapted self-report measure from Janssen I, Hanssen M, Bak M et al. Discrimination and delusional ideation. B J Psych 2003, 182:71-76. Participants answer 'yes' or 'no' to whether they had experienced discrimination in their lifetime because of their skin color; ethnicity; gender; age; appearance; disability; sexual orientation; religion; or other reason. Total perceived discrimination is calculated as the total number of "types of discrimination" that are endorsed. The Perceived Discrimination Scale will be used to examine whether perceived discrimination is a predictive factor for transition to psychosis.
    e. **The Pubertal Development Scale (PDS):** This is a self-assessment instrument composed of five questions pertaining to growth spurt, body hair, and changes in skin for both sexes, rated on 5-point scales: "not yet started" (scored as one point), "barely started" (two points)", "definitely started" (three points)", "seems complete" (four points), "I don't know" (treated as missing values). On a similar scale, males also rate their development regarding changes in voice and facial hair growth, while females rate breast growth. Females also state whether they have begun to menstruate. The PDS will be used to assess physical changes during puberty.
    f. **Past/Current Medications, Psychosocial Treatment, and Adverse Events:** Data will be collected from participants and parents on medication use at each visit, supplemented by pharmacy and medical records as available. Data will also be collected on the start and stop

dates of participant past and current medical and psychiatric services being received. Adverse events will be assessed at each visit.

g. **Other Diagnoses:** The psychosis, substance use, and mood modules will be completed from the Structured Clinical Interview for DSM V (SCID) will be utilized to confirm if participants meet criteria for other diagnoses
h. **Negative Symptoms:** Negative symptoms will be assessed utilizing 16 items from the Negative Symptom Inventory-Psychosis Risk which assess the 5 NIMH consensus domains (anhedonia, avolition, asociality, alogia, blunted affect) [7]
i. **General Psychopathology:** General psychopathology will be assessed utilizing the Brief Psychiatric Rating Scale (BPRS)
j. **Affective Symptoms and Anxiety Symptoms:** Depression will be assessed utilizing the Calgary Depression Scale for Schizophrenia (CDSS) [8] and Overall Anxiety Severity and Impairment Scale (OASIS) will be used for anxiety severity, supported by its long use and quick administration along with good psychometric properties and its coverage of cognitive symptoms of anxiety that may be useful for sensitivity to change
k. **Global Functioning:** Functioning will be assessed utilizing the Global Functioning: Social and Role scales that were developed specifically for CHR [9].
l. **Global Change:** The Patient Global Impression Scale - Severity (PGI-S) will be utilized to assess patient reported impression of severity of illness.
m. **Substance Use:** Substance use will be evaluated using (i) The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).
n. **Suicidality:** Suicidality will be assessed utilizing the Columbia-Suicide Severity Rating Scale (C-SSRS) a suicide severity rating scale that measures four constructs: the severity of ideation, the intensity of ideation, behavior and lethality.
o. **The Perceived Stress Scale (PSS):** The PSS is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives.
p. **8-Item PROMIS for Sleep Questionnaire:** This is used to measure self-reported perceptions of sleep quality, depth, and restoration within the past seven days. This includes perceived difficulties falling asleep and staying asleep, as well as sleep satisfaction.
q. **Cognition:** Cognition will be assessed using the Penn Neurocognitive Battery (PennCNB) and the Wechsler Abbreviated Scale of Intelligence, 2nd Ed. (WASI-II). The Wide Range Achievement Test (WRAT) will be used to assess exclusion criterion for low overall cognitive ability.
r. **Ecological Momentary Assessments (EMA):** Digital phenotyping and EMA will be offered on participants' personal smartphones (Apple or Android) by installing the mindLAMP platform [5], [6]. MindLAMP is an optional procedure that will be offered to all participants. MindLAMP is a smartphone app that collects information through audio recording (audio diaries), daily surveys, and passive sensing. Audio diaries and daily surveys include asking participants to record a two-minute audio diary about their recent experiences, events, and context and to complete a very brief EMA symptom survey (total time < 2 minutes) on their smartphone daily for 52 weeks. For passive sensing the smartphone app will collect data which includes physiological data, geolocation data, offers surveys that measure and stabilize symptoms, and features games that assess cognition. Participants will be offered an introductory video to explain how the app works. Participants can choose from the following four participation options (1) mindLAMP audio diaries, surveys, passive sensing including geolocation (2) mindLAMP audio diaries, surveys, passive sensing NOT including geolocation,

(3) mindLAMP audio diaries and surveys only without passive sensing, or (4) choose not to participate in mindLAMP.

s. **EM Wrist Actigraphy:** Participants will be asked to wear a device on their wrist (the Axivity AX3) which will track their activity, such as step count, for the first year of the project. This is an optional procedure that will be offered to all participants.
t. **Vital Signs:** Collection of height and weight, blood pressure, heart rate, and body temperature
u. **Current Health Status Form:** This form will be completed prior to biological sample collection and captures sleep and wake times, last meal and/or beverage, tobacco and/or marijuana use, last menstrual period, acute inflammation, and current day activity status.
v. **Magnetic Resonance (MR)-Based Imaging:** The study will collect three 3T MRI-based measures as biomarkers: sMRI, for brain morphometrics and surface generation, resting state blood oxygen level dependent (BOLD) functional MRI for rsfMRI, and dMRI for tissue microstructure estimation and structural connectivity analysis. The proposed protocol is aligned with the simultaneous multi-slice ("multiband") Human Connectome Project (HCP) style of acquisition but adapted to create a reasonably harmonized acquisition protocol for a multi-site, multi-vendor study. All participating sites have 3T scanners with either 32 or 64-channel receiver coils and the capacity to conduct the 60-minute protocol procedures.
w. **Electroencephalography (EEG):** Identically configured Brain Products actiCHamp+actiCAP 64 channel systems will be placed by NeuroSig at all ProNET sites to record EEG. Consistent stimulus presentation will be achieved by programming tasks for specific hardware developed by NeuroSig that cannot be modified or inadvertently altered. Task conditions showing the greatest promise in prior analyses are implemented, including i) 2-stimulus MMN/3-stimulus visual oddball task, and ii) 3-stimulus auditory oddball task. The MMN task will present a pseudo-random sequence of frequent (90%) tones (633 Hz, 50ms) and infrequent (10%) double deviant (1000 Hz, 100ms) tones using a fixed 500ms stimulus onset asynchrony (SOA). Participants will be told to ignore the tones while performing the visual oddball task. Onsets of auditory and visual stimuli will be jittered to avoid ERP overlap. Visual and auditory oddball tasks will be identical to those from NAPLS-2 and have rare target and novel stimuli (10% each) and frequent (80%) standards. Each oddball task is presented in 4 blocks, lasting either 5 (MMN/visual) or 3 (auditory) minutes each. Resting EEG will be recorded with eyes open and closed (2 min each). With setup (15-20 min), instructions (5 min), recording (50 min), and breaks, sessions should last 75-90 minutes Use of an active electrode, high-impedance EEG system like actiCHamp will minimize participant discomfort during short EEG recordings with frequent breaks, increasing follow-up EEG session retention.
x. **Genomics and Fluid-Based Biomarkers:** The study will obtain blood (< 50 mL at each time point, an amount that does not pose health risks for persons ages 12-30, and no more than 3ml/kg) and saliva specimens (at baseline and 2 month follow-up). Blood will be processed at sites for serum (3 cryovials), plasma (6 cryovials), leukocytes (1 cryovial) and whole blood (3 cryovials). Each cryovial contains 1 mL of sample. Two cryovials of saliva will be collected at 3 time points an hour apart at using passive drool. Aliquoted blood specimens will be stored in a -80 freezer then bulk shipped every 6 months on dry ice to the National Institute of Mental Health (NIMH) Repository & Genomics Resource (NRGR). A single tube of blood will be sent to a local lab for CBC/differential. The NRGR will extract DNA from leukocytes. Portions of the extracted DNA may be sent to the Broad Institute for genomic analyses in batches as sufficient numbers of study subjects are ascertained. One saliva cryovial from each of the 3 time points will be sent from the NRGR to a contracted laboratory such as Salimetrics for cortisol

levels in batches as sufficient numbers of study subjects are ascertained. One cryovial of plasma will be sent from the NRGR to a (as yet to be determined) facility for inflammatory biomarker analyses in batches as sufficient numbers of study subjects are ascertained. Participants will receive instructions regarding food/beverage/drug consumption. Information will be recorded about potential confounders (drug, food, and fluid intake, acute illnesses, weight, height, exercise, sleep, and vital signs). The NRGR will store the unused cryovials and DNA. The NRGR will share the specimens with other investigators meeting NIMH-determined requirements.

y. **Natural Language Processing/Speech Acoustics/Face Expression:** Speech/language and face expression data will be collected during a video recorded 30 minute "welcoming" open-ended interview preceding the initial PSYCHS interview, as well as from the PSYCHS interview itself and any other interviews and assessments that have audiovisual recording, including clinical interviews, cognitive tests, and digital capture using smartphones. Audio recordings will be transcribed using HIPAA-compliant services such as TranscribeMe or Zoom or similar HIPAA-compliant software, and pseudo-anonymized using manual or automated pseudo-anonymized methods. Zoom allows diarization or separation of voice streams. For interviews conducted in languages other than English, transcripts will be done in the native language. Open source software such as PRAAT will be used to extract speech acoustic data that cannot be used to identify individuals. Open source software such as OpenFace will be used to extract face expression data (face action unit amplitude, eye gaze, head pose) that also cannot be used to identify individuals.

z. **Psychosis Polyrisk Score (PPS):** The PPS is a self-report measure used to assess known environmental risk factors for psychosis.

3. **Visit 3 (month 1)** will take approximately 2-3 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 Schedule of Events.
    a. **Premorbid Adjustment Scale (PAS):** The PAS will be used to assess premorbid functioning across developmental periods and across a number of domains. The "premorbid" period for PAS purposes is the period ending six months prior to the participant first meeting CHR criteria.
    b. Outcome measures collected are as described in assessments above

4. **Visit 4 (month 2)** will take approximately 6 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments and Table 3.0 ProNET Healthy Control Schedule of Assessments. The assessment is expected to be completed over 2-3 days within the same week.
    a. Outcome measures and biomarkers collected are as described in assessments above.

5. **Visit 5 (month 3)** will take approximately 2-3 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments.
    a. Outcome measures and biomarkers collected are as described in assessments above.

6. **Visit 8 (month 6),** will take approximately 2-3 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET Schedule of Assessments.
    a. Outcome measures and biomarkers collected are as described in assessments above.

7. **Visit 6 (month 4), visit 7 (month 5), visit 9 (month 7), visit 10 (month 8), visit 11 (month 9), visit 12 (month 10), and visit 13 (month 11)** will take less than 1 hour to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET Schedule of Assessments.
    a. Outcome measures collected are as described in assessments above.

8. **Visit 14 (month 12)** will take approximately 3-4 hours to complete for CHR participants or 1-2 hours to complete for HC participants and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments and Table 3.0 ProNET Healthy Control Schedule of Assessments.
    a. Outcome measures collected are as described in assessments above.

9. **Visit 15 (month 18)** will take approximately 2 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments.
    a. Outcome measures collected are as described in assessments above.

10. **Visit 16 (month 24)** will take approximately 4 hours to complete for CHR participants or 1-2 hours to complete for HC participants and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments and Table 3.0 ProNET Healthy Control Schedule of Assessments.
    a. Outcome measures collected are as described in assessments above.

11. **Conversion Assessment:** If a participant is thought to have converted to psychosis at any point in the ProNET study, they would return to the site for a conversion assessment. This assessment will take approximately 3 hours to complete and includes the following procedures and assessments as detailed in Table 2.0 ProNET CHR Schedule of Assessments.
    a. Outcome measures collected are as described in assessments above.

For all visits sites will attempt to adhere to a preferred order for data collection where possible but it will not be considered a protocol deviation if the preferred order is not followed.

1. Informed consent must be completed prior to assessment collection, and would be a protocol deviation if not correctly obtained
2. Clinical interviews may be completed by phone or video conferencing and do not require participants to come to the research site
3. It is preferred that blood and saliva samples be collected on separate days or if not possible that saliva is collected prior to the blood sample
4. Blood samples are collected as close as possible to 12 PM
5. Vital signs should be collected just prior to the blood sample collection
6. EEG should not be completed after the clinical or cognition assessments

Visits should be completed as close as possible to the target visit date. Sites should attempt to schedule all participant visits within the visit window, but it will not be considered a protocol deviation if the visit is completed outside the visit window. If a participant returns for a visit outside of the visit window, the visit should still be completed and the study team contacted to discuss data entry guidelines. The visit windows are +/- 7 days for the monthly visits from Month 1 through Month 11 (with the exception of month 2 which is only +7days) and +/-14 days for Month 12, Month 18 and Month 24 visits.

Table 2.0 CHR ProNET CHR SCHEDULE OF ASSESSMENTS

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 8	Visit 14	Visit 15	Visit 16	Conversion
Month	-3 to -1	Month 0	Month 1	Month 2	Month 3	Month 4, 5, 7, 8, 9, 10, 11	Month 6	Month 12	Month 18	Month 24	
Visit Window[1]			+/-7 DAYS	+7 DAYS	+/-7 DAYS	+/-7 DAYS	+/-7 DAYS	+/-14 DAYS	+/-14 DAYS	+/-14 DAYS	
Informed consent	30										
Inclusion/exclusion criteria review	30										
Past/current meds, Psychosocial Treatment, Adverse Events	5	5	5	5	5		5	5	5	5	5
Sociodemographics		10									
Health Conditions (Medical History/Psychiatric History)	15										
Structured Clinical Interview for DSM-5 Personality (SCID-dPQ))	10										
Structured Clinical Interview for DSM-5 (SCID) (Psychosis, Mood, Substance Use)		60						45		45	45
Traumatic Brain Injury (TBI) Screening[4]	15										
Family Interview for Genetic Studies (FIGS)	15										
PSYCHS[5]	30	30	30	30	30		30	30	30	30	30
The Social and Occupational Functioning Scale (SOFAS)[5]	15	5	5	5	5		5	5	5	5	5
Premorbid Adjustment Scale (PAS)			15								
Perceived Discrimination		2									
Puberty Development Scale (PDS)		3									
Penn Neurocognitive Battery (PennCNB)[3]		30		10			30	30		30	
Wechsler Abbreviated Scale of Intelligence, 2nd Ed. (WASI-II)		15								15	
Premorbid IQ (reading accuracy)		5									
EEG		105		105							
MRI		75		75							
MindLamp EMA set up		30									
Active Data Collection: 20-Item Daily Ecological Assessment - Daily 2 mins/day after initial orientation for 52 weeks[2]			60	60	60	60	60	60			
Actigraphy Collection (Wrist)[2]		5	5	5	5	5	5	5			
Vital Signs (height, weight, HR, BP, temp)		3		3							
Current Health Status		5		5							
Saliva collection (ELISA)		10		10							
Blood collection (Biospecimen Preanalytics and Quality Assurance, CBC with Differential, Buffy Coat - DNA, Plasma, Serum, Whole Blood)		10		10							
Language Content & Structure and Speech Acoustics: Open-ended (OE) Interviews		30		30							
Negative Symptom Inventory-Psychosis Risk		15	15	15	15		15	15	15	15	15
Calgary Depression Scale for Schizophrenia (CDSS)		15	15	15	15		15	15	15	15	15
Overall Anxiety Severity & Impairment Scale (OASIS)		5	5	5	5		5	5	5	5	5
The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)		5		5			5	5	5	5	5
Columbia-Suicide Severity Rating Scale (C-SSRS)		5		5			5	5	5	5	5
Perceived Stress Scale (PSS)		5	5	5	5		5	5	5	5	5
Global functioning: Social and Role		15	15	15	15		15	15	15	15	15
8 - item PROMIS for sleep		5		5			5	5	5	5	5
Brief Psychiatric Rating Scale (BPRS)[3]		5	5	5	5	20	5	5	5	5	5
The Patient Global Impression Scale - Severity (PGI-S)		5	5	5	5		5	5	5	5	5
Psychosis Polyrisk Score (PPS)		5									
TOTAL TIME TO DATE	**165**	**523**	**185**	**433**	**170**	**85**	**215**	**260**	**120**	**210**	**165**
TOTAL TIME AT VISIT (DELETE EMA ASSESSMENT AS COMPLETED OUTSIDE THE VISIT)	**165**	**523**	**125**	**373**	**110**	**25**	**155**	**200**	**120**	**210**	**165**

[1] Visit windows are for scheduling puposes only and if participants return for an assessment outside the window the assessment should still be completed

[2] Optional Assessments

[3] At month 2 only a partial PenCNB will be completed and includes Processing Speed, Relational Memory, and Verbal Learning;

[4] If a TBI is known or reported during the screening, the TBI screening instrument needs to be completed

[5] If conversion is suspected from the results of the BPRS a PSYCHS may be administered

[6] If the screening PSYCHS and SOFAS was completed within 21 days of the last completed baseline assessment, the baseline PSYCHS and SOFAS will not need to be completed at baseline

Table 3.0 ProNET HEALTHY CONTROL SCHEDULE OF ASSESSMENTS

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Month	-3 to -1	Month 0	Month 2	Month 12	Month 24
Visit Window[1]			+7 DAYS	+/-14 DAYS	+/-14 DAYS
Informed consent	30				
Inclusion/exclusion criteria review	30				
Past/current meds, Psychosocial Treatment, Adverse Events	5	5	5		
Sociodemographics		10			
Health Conditions (Medical History/Psychiatric History)	15				
Structured Clinical Interview for DSM-5 Personality (SCID-dPQ))	10				
Structured Clinical Interview for DSM-5 (SCID) (Psychosis, Mood, Substance Use)		60		45	45
Traumatic Brain Injury (TBI) Screening[4]	15				
Family Interview for Genetic Studies (FIGS)	15				
PSYCHS[5]	30	30	30	30	30
The Social and Occupational Functioning Scale (SOFAS)[5]	15	5	5	5	5
Premorbid Adjustment Scale (PAS)					
Perceived Discrimination		2			
Puberty Development Scale (PDS)		3			
Penn Neurocognitive Battery (PennCNB)[3]		30	10		
Wechsler Abbreviated Scale of Intelligence, 2nd Ed. (WASI-II)		15			
Premorbid IQ (reading accuracy)		5			
EEG		105	105		
MRI		75	75		
MindLamp EMA set up		30			
Active Data Collection: 20-Item Daily Ecological Assessment - Daily 2 mins/day after initial orientation for 52 weeks[2]			120	600	
Actigraphy Collection (Wrist)[2]		5	10	50	
Vital Signs (height, weight, HR, BP, temp)		3	3		
Current Health Status		5	5		
Saliva collection (ELISA)		10	10		
Blood collection (Biospecimen Preanalytics and Quality Assurance, CBC with Differential, Buffy Coat - DNA,Plasma, Serum, Whole Blood)		10	10		
Language Content & Structure and Speech Acoustics: Open-ended (OE) Interviews		30	30		
Negative Symptom Inventory-Psychosis Risk		15	15		
Calgary Depression Scale for Schizophrenia (CDSS)		15	15		
Overall Anxiety Severity & Impairment Scale (OASIS)		5	5		
The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST		5	5		
Columbia-Suicide Severity Rating Scale (C-SSRS)		5	5		
Perceived Stress Scale (PSS)		5	5		
Global functioning: Social and Role		15	15		
8 - item PROMIS for sleep		5	5		
Brief Psychiatric Rating Scale (BPRS)		5	5		
The Patient Global Impression Scale - Severity (PGI-S)		5	5		
Psychosis Polyrisk Score (PPS)		5			
TOTAL TIME TO DATE	165	523	498	730	80

[1] Visit windows are for scheduling puposes only and if participants return for an assessment outside the window the assessment should still be completed
[2] Optional Assessments
[3] At month 2 only a partial PenCNB will be completed and includes Processing Speed, Relational Memory, and Verbal Learning;
[4] If a TBI is known or reported during the screening, the TBI screening instrument needs to be completed
[5] If the screening PSYCHS and SOFAS was completed within 21 days of the last completed baseline assessment, the baseline PSYCHS and SOFAS will not need to be completed at baseline

12. STATISTICAL ANALYSIS

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

The study is powered using a conservative 3 time-point repeated measures biomarker-behavior multivariate discovery/replication model. The biomarker/clinical features would be evaluated as multivariate index. There is power for a range of effect sizes, while assuming a conservative zero correlation across repeated measures. Other estimates are also conservative: the study retains 80% of the sample for the longer-term outcomes and computes a randomized split-half training-test cross-validation (n=416 per set), which would be the least powered discovery/replication analysis. In addition, a simulation analysis was performed testing the performance of a linear kernel support-vector machine (SVM) to separate an event sample from a non-event population using 5-fold cross-validation. Results indicate that with the proposed sample SVM produces a favorable BAC>70% for an event rate of >0.2 and 10% moderately predictive features in a data space of up to 5000 features.

13. SPECIMEN BANKING

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

Blood and saliva samples will be sent to the National Institute of Mental Health (NIMH) Repository & Genomics Resource (NRGR). DNA samples derived from blood, saliva samples, and blood samples will also be sent to service providers for analyses of DNA, cortisol, and metabolites. Study information, blood, and saliva samples will be identified by a number only, and no identifying information will be included with any of the samples.

Samples and study information not used for planned analyses will be stored indefinitely for as yet undetermined analyses. NIMH will make these resources available to other scientists who want to do research that has been reviewed and approved by an NIMH data access committee.

14. DATA MANAGEMENT AND CONFIDENTIALITY

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

The sources of data collected are:

- Text/numeric data from interviews, self-report questionnaires, and cognitive tasks
- Blood and saliva collection
- DNA collection
- MRI imaging data
- EEG data
- Ecological Momentary Assessment/Digital Phenotyping
- Video and Audio Capture of face, speech, and voice

The information included in those data sources are:

- Text/numeric data includes demographics, psychiatric diagnosis, positive symptoms, negative symptoms, affective symptoms, anxiety symptoms, substance abuse, cognition, medication, treatment, research participation, and consent history.

- Blood and saliva collection includes blood samples to be analyzed for a CBC with differential and inflammatory biomarkers. Saliva is to be analyzed for cortisol.
- DNA will be sequenced. Polygenic risk scores will be generated from the results.
- MRI imaging data include structural, resting-state functional, and diffusion data
- EEG data include P300 to visual and auditory oddball stimuli and mismatch negativity
- Ecological Momentary Assessment/Digital Phenotyping will include: brief surveys; activity levels, sleep, and social rhythms via sensors like accelerometer and geolocation; and social context and local environments via anonymized call/text logs, Bluetooth density, and geolocation.
- Video and Audio Capture will include facial emotional expression, vocal emotional expression, and text processing of speech and language expression

Data from each of these sources will be stored at the ProNET Secure Data Lake (SDL) at Yale:
- alphanumeric string data
- MRI
- EEG
- Ecological Momentary Assessment/Digital Phenotyping
- Video and Audio Capture of face, speech, and voice

Data from other sources will be initially stored as follows:
- Blood will be biobanked at the NRGR for future analysis.
- Saliva will be biobanked at the NRGR and shipped for cortisol analysis to a contracted laboratory such as Salimetrics.
- DNA will be shipped from the NRGR to the Broad Institute for analysis.

Data from each source will be stored indefinitely at the ProNET Secure Data Lake (SDL) at Yale, following best practices for data security using secure firewalls.

Global Unique Identifier

The ProNET study will use NDA's global unique identifier (GUID) for all participants in this study. The GUID is a common human participant identifier across NDA Collections and is a secure approach to increasing the quality of cross-study analyses. The GUID will be requested by the local investigator site utilizing the participant information required (first name, middle name, last name, DOB, city of birth, sex at birth). If the participant's information needed to generate a GUID is not collected or missing, a pseudo GUID will be requested for those participants. The PII needed to create the GUID is kept at the site only and is not transmitted to Yale or NDA. The software processes the identifiers into several intermediary codes using a one-way hash function (a cryptographic algorithm) and transmits the codes (hashes) in a secure manner to a secure NDA data enclave, where an alphanumeric GUID is linked to the hash codes. NDA returns the GUID to the local site, which will enter the GUID into the participant's record at the ProNet Data Lake at Yale.

Data Flow

Data stored in the ProNET Secure Data Lake, apart from direct identifiers and audio and video data, will be sent to a secure staging area at the NIMH Data Archive (NDA) where the NIMH-funded Data Processing Analysis and Coordinating Center (DPACC) will perform quality assurance and mask (deidentify) all dates. After these steps are completed, the data will be sent to a Collaboration space within NDA and then to the NDA proper, where it will be stored indefinitely.

Data Access

The ProNET PIs and their hub administrative staff will manage a secure system of tiered access to data in the ProNET Secure Data Lake (SDL) as follows:
- Investigators at each contracted site will have access including download privileges in the ProNET SDL to pseudo-anonymized data collected at their site.

- All investigators at all contracted ProNET sites will have analytic access as needed in the ProNET SDL to all pseudo-anonymized data from all sites as approved by the ProNET PIs and their hub administrative staff.
- Investigators affiliated with the ProNET administrative hub at Yale, investigators from the NIMH-mandated collaborating DPACC and PRESCIENT projects for quality control purposes in analyses of audio and video files, the DPACC data monitor, contracted sites Northwell and UCLA, and ProNET Core Directors at contracted sites Calgary, Kings College London, BIDMC, Emory, UCSF, and UNC with demonstrated need to access identifiable data in order to manage the ProNET study will have access in the ProNET SDL as approved by the ProNET PIs and their hub administrative staff.
- Subcontracts containing data sharing language will be negotiated between Yale and all ProNET sites.

The NDA Secure Staging Area will allow access to data as follows:

- The data will be accessed only by the NIMH-selected Data Processing Analysis and Coordinating Center (DPACC) at Harvard/Brigham and Women's.

The NDA Collaboration Space area will allow access to data as follows:

- Access to data stored in the NDA Collaboration space will be controlled by the NDA and by the Accelerating Medicines Partnership - Schizophrenia NIMH Clinical High Risk Steering Committee.

The NDA proper will allow access to data as follows:

- Access to data stored in the NDA proper will be controlled by a US National Institute of Mental Health data access committee and not by the ProNET Hub at Yale or by the local data collection site. Investigators requesting shared data must be affiliated with an NIH-recognized research institution that maintains an active Federal-Wide Assurance (FWA) and complete and submit a Data Use Certification approved by an authorized institutional business official with signature authority. This request will then be reviewed by the Data Access Committee. GPS location data will be additional protected by requiring that investigators receive local IRB approval prior to access.

The ProNET principal investigators Scott Woods at Yale, John Kane at Northwell, and Carrie Bearden at UCLA and the ProNET administrative hub at Yale, Northwell, and UCLA are responsible for receipt and transmission of data and specimens.

Security of Data during storage use and transmission.

- The ProNET Secure Data Lake at Yale will employ fully HIPAA- compliant XNAT, REDCap, and YaleSecureBox resources (https://redcapynh-p11.ynhh.org, or similar HIPAA-compliant REDCap, http://xnat.yale.edu, https://yalesecure.app.box.com) for data-sharing, data storage and transfer. The clinical and neuroimaging data-sharing and organization will use a 2-prong neuro-informatics strategy deployed at Yale: i) Clinical behavioral data will be stored and shared via the REDCap database; ii) The pseudo-anonymized neuroimaging data and other multi-modal data sources will be stored and shared via the Extensible Neuroimaging Archive Toolkit (XNAT), which readily integrates with REDCap. REDCap is a free, secure, web-based application designed to support data capture for research studies (http://project-redcap.org). The system was developed by a multi-institutional consortium initiated at Vanderbilt University. Importantly, the REDCap database is fully compatible with the XNAT system, which is an informatics platform for managing, exploring, and sharing neuroimaging data (http://www.xnat.org), developed at Washington University in St. Louis. Specifically, XNAT is designed to facilitate quality control procedures and provides secure access to and storage of both clinical and neuroimaging data.

XNAT follows a 3-tier architecture that includes a data archive, user interface, and middleware engine. Data can be entered into the archive as XML or through data entry forms. Newly added data are stored in a virtual quarantine until an authorized user has validated it. XNAT subsequently maintains a history profile to track all changes made to the managed data. User access to the archive is provided by a secure web application. The web application provides a number of quality control and productivity features, including data entry forms, data-type-specific searches, searches that combine across data types, The detailed reports, and listings of experimental data, upload/download tools, access to standard laboratory workflows, and administration and security tools. The research team will upload pseudo-anonymized DICOM and/or NIFTI images. These images will be maintained via the XNAT database on the Yale servers and storage systems. As noted, the clinical information captured in REDCap can be readily integrated into XNAT for joint analyses. Furthermore, the XNAT database is deployed as part of the Human Connectome Project, providing a well-tested and robust long-term strategy for data management and pipeline workflow as proposed here.

- Data from the four sources below will be transferred directly and securely from sites to the ProNET SDL at Yale as specified above:
    - alphanumeric string data
    - MRI
    - Ecological Momentary Assessment/Digital Phenotyping
    - EEG data

  Data from the sources below will transferred to the ProNET SDL indirectly:

    - Blood samples will be shipped from the NIMH Repository to contracted laboratories for quantification of inflammatory, lipid, or other analytes. Pseudo-anonymized extracted alphanumeric features will be securely transferred to the ProNET SDL.
    - Saliva will be shipped for cortisol analysis from the NRGR to a contracted laboratory such as Salimetrics. Pseudo-anonymized extracted alphanumeric features will be securely transferred to the ProNET SDL.
    - DNA will be shipped from the NRGR to the Broad Institute for analysis. The resulting raw genomic data will be stored at the NDA. Pseudo-anonymized alphanumeric extracted features will be securely transferred to the ProNET SDL.
    - Video and Audio Capture of face, speech, and voice will be captured by a HIPAA-compliant Zoom account at Yale. A subset of audio samples will be transferred from ProNET SDL to the HIPAA-complaint ProNET vendor TranscribeMe for manual transcription, with secure transfer of transcripts back to ProNET SDL. Only the transcripts will be submitted to the NDA. Original audio and video files will not leave the ProNET SDL.
    - Penn CNB cognition data will be captured using the secure WebCNP computerized neuropsychological testing system operated by the ProNET contracted site at the University of Pennsylvania and transferred securely to the ProNET SDL.

Business agreements/subcontracts will be negotiated between Yale and NeuroSig, the NIMH Repository, the Broad Institute, and TranscribeMe.

15. DATA AND SAFETY MONITORING PLAN

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

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

Part I: Elements of the Data and Safety Monitoring Plan

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

N/A

Part II: Data and Safety Monitoring Board or Committee

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

N/A

16. WITHDRAWAL OF SUBJECTS

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

All sites will attempt to engage CHR participants for the length of the ProNet study. Site investigators may remove a participant from the study at any time if they feel that it is not in their best interest to continue. Participants may also choose to withdraw consent at any time. If a participant requests to withdraw from the study, they will be asked if the site can recontact them during the original 2-year participation period to determine if they would be interested in continuing in the data collection. If the participant indicates no, the site will not have further contact with the participant regarding this study. When a participant requests to be withdrawn from the study, they can allow their already collected data and samples to continue to be utilized/analyzed or they can request that their data is removed, and their stored samples are destroyed. If the data already collected has already been analyzed, it will not be possible to remove their data from the analysis.

17. RISKS TO SUBJECTS

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

The overall risks for the ProNET study are minimal and listed below:

1. Confidentiality: There is a potential risk that protected health information collected during the course of the study may be disclosed to others.
2. Stigma: There is a potential risk that participants will be subjected to stigma and undue anxiety from identification as "at risk" of a serious mental disorder.
3. Distress: There is a potential risk that the participants may find the study questions and procedures tedious, or that they may be distressed by the discussion of personal issues.
4. Body fluid acquisition: There is a potential risk of pain, bruising and infection from the blood draw. Saliva collection are low risk procedures.
5. Genotyping: DNA will be stored at the NIMH Repository and analyzed at the Broad Institute. Participants consent to biobanking and sharing DNA and the results of DNA analysis with other scientists. While DNA specimens are pseudo-anonymized there is a risk that the participant's identity may be discerned by investigators through matching their unique DNA pattern.
6. MRI: MR imaging is considered to be a medically safe procedure. There are no reports of medically adverse reactions to MRI sequences. However, MRI acquisition involves exposure to a strong magnet. Thus, the primary physical risk associated with MRI is the risk of injury associated with metal objects being drawn into the magnet. These objects could be internal (e.g., surgical implants) or external items. In addition, some participants may experience transient peripheral nerve stimulation or nausea in the bore of the magnet. Nausea can be minimized by stabilizing the head. Some participants may find the confinement in the MRI machine to be claustrophobic, physically uncomfortable, or noisy. Raw MRI files contain identifiable information relating to facial and ear features.
7. EEG: EEG is recorded by affixing EEG electrodes to the scalp using electrodes embedded in a nylon cap. To reduce impedances for adequate signal-to-noise ratios during EEG recording,

the scalp is abraded slightly with a blunt probe. This may cause skin irritation and/or mild discomfort or lead to local skin infections. Thus, some participants may find the psychophysiological procedures uncomfortable. There is also a very low risk of developing an allergic reaction to the electrode conductive gel, which contains chemicals similar to human sweat. Generally, in EEG laboratories, the risk of irritation, infection, or allergic reaction is small (less than 1%). Raw EEG data contains no identifying information.

8. EMA / Digital Phenotyping:
    a. Confidentiality: No information will be stored on participants' phones so there is no risk to the participant if their mobile phone is lost or stolen. Before being transmitted, all data is encrypted on the phone to a degree where the phone itself cannot read the data – offering further protection if the phone is lost. Also, the application is password protected so any user data would not be revealed if the phone is stolen. Encrypted information from survey responses and passive data will be sent and stored electronically using HIPAA-compliant data management software (REDCap) on HIPAA compliant servers. Responses from individual participants will be identified by a randomized number and contain no personal identifiable information. Geolocation information, which can be identifying will be stored at the NDA and made available only to researchers who submit the following to the NDA (a) and NDA data use agreement approved by their institutional signing official and (2) documentation of approval from their local IRB to access geolocation data. Participants are given the opportunity to opt-out of geolocation data collection at the time of consent. While the geolocations data are pseudo-anonymized there is a risk that the participant's identity may be discerned by investigators through analysis of their geolocation. Like any technology system, it is possible that this system will be hacked and the information stolen. However, all software used will be continuously maintained to industry standards.
    b. Another potential risk is if a participant is observed using this smartphone application, then there is the chance that an observer might note them taking surveys about mental health. However, as these mobile surveys and passive data assessments do not mention any information about the study itself and the questions are about many diverse symptoms it is very unlikely that an observer might be able to deduce these survey are part of a research study. Numerous psychiatry symptoms tracking applications are already commercially available on the Apple iTunes or Android Google Play stores and already used by thousands of people on a daily basis so even if observed using this application, it would be difficult for an observer to deduce it is part of a research study or that the participant suffers from a psychosis spectrum illness.
    c. While there is the potential for risk of worsening mental or emotional state with any intervention or clinical study, there is no evidence that use of observational monitoring or tracking via smartphone is associated with such risk. Previous experience conducting EMA research with clinical high risk and first episode psychosis participants and has found that these participants are interested and excited to use technology and personally we have not seen any adverse events. All consented participants are already receiving mental health care and the app contains touch screen buttons to allow participants to call the study team or emergency services at any time – providing an additional safety net. All participants will be educated on how to delete the app at any time which will end data collection if they feel it is causing them distress or harm.
    d. Another potential risk is that while participants use the app to fill out surveys while driving, they may become distracted and cause an accident resulting in serious harm

or death. Federal and state laws forbid active use of apps while operating a motor vehicle and we will warn and inform all participants about this.

e. The risk associated with the Axivity AX3 device are expected to be minimal and could include a rash or psychological stress from wearing a device. The device collects no personal or health information so any data breach would not compromise personal or health data.

9. Face and Voice Expression / NLP. Raw audio and video files and speech transcripts contain identifying information. Individuals are directly identifiable from raw video and audio. In addition individuals could potentially disclose identifying data in the content of the speech, revealing something that breaches confidentiality or even is potentially incriminating. There is a potential risk that confidential information collected during the course of the study may be disclosed to others.

Overall the identified risks above will be managed by:

1. Confidentiality: Each site will act as a data controller for their own PHI. The hub's informatics team is available and resourced to guide and support sites in this task. Personal data needed to contact the subject will be securely stored only at the site and separate to the main network databases. Confidentiality of personal data transferred to the hub at Yale, which will also act as a data controller, will be maintained by assigning each participant a study number, and coding all data coded with that number, using the NIH GUID tool. Data will be transferred from the sites to and stored in the GDPR HIPAA- compliant ProNET Secure Data Lake servers: YaleREDCap (https://redcapynh-p11.ynhh.org or similar HIPAA-compliant REDCap), XNAT@Yale (http://xnat.yale.edu), and Yale Secure Box (https://yalesecure.app.box.com). All computer databases are password protected to industry standards for level of data risk, and any hard copies of all data and records will be stored in locked filing cabinets in locked rooms in security-protected buildings.
   Pseudo-anonymized versions of and pseudo-anonymized features extracted from the data will be made available to appropriately-credentialed institutional investigators, including the NIMH-selected Data Processing Analysis and Coordinating Center at Harvard/Brigham and Women's. Individuals and their institutions receiving data will be required to pledge that they will not reshare data except as specified in their data sharing agreement or attempt to reidentify participant's data. All investigators who obtain access to shared data via the NDA must agree to the NDA Data Use Certification which states that they agree to not attempt to identify individual participants from whom data within a dataset was obtained. Any attempt to do so could result in denial of further access to NDA data and in other actions. All study personnel will be certified to conduct research with human participants and will be aware of the importance of maintaining strict confidentiality.
2. Stigma: Risks of stigma and undue anxiety from identification as "at risk" of a serious mental disorder will be minimized in the following ways:
   a) Information regarding possible outcomes and causes will be routinely provided. Participants will be informed about possible outcomes, including remission, persistent symptoms, or worsening of symptoms. They will be informed that causes of symptoms include a normal adolescent or early adult maturation, a reaction to a life stressor, a symptom of drug use, symptoms of a metabolic disorder, the symptoms of a mood disorder or anxiety disorder, or the early warning signs of affective disorder or schizophrenia.
   b) Study participants who are judged to be in need of psychiatric or psychological evaluation/treatment, and are not currently receiving treatment, will be referred as clinically indicated. All participating sites have protocols for referral to psychiatric services.

c) In addition, to minimize risk of undue anxiety related to uncertainty of diagnosis at screening we will also conduct a careful systematic diagnostic interview and cognitive evaluation to determine whether there is an active diagnosable condition.

3. Distress: The risk that the participants may find the study questions and procedures tedious, or that they may be distressed by the discussion of personal issues will be minimized by having a study staff person monitor the participant's experiences during the study procedures, and by having a study clinician familiar with the participant available to assist the participant if she or he becomes distressed by study procedures. In addition, participants will be told that they may decline to answer any questions or discuss any issue if they do not want to or if they find it distressing. Efforts will be made to make the study assessment procedures as pleasant as possible for the participant, and to detect and address any problems with evaluation procedures.
4. Blood draw: The risks of the blood draw include pain, bruising, and risk of infection that will be minimized by using aseptic/clean techniques, having blood drawn by an experienced phlebotomist, and offering the participant use of a topical anesthetic at the time of the blood draw. Less than 50mL is drawn at the study visit, and amount that is safe for persons aged 12 and older.
5. Genotyping: During this study DNA will be collected from participants and will be biobanked at the NIMH Repository. Both NIMH and the Broad Institute have implemented measures to protect participants' anonymity, including requiring scientists who request DNA or DNA results to agree to not perform analyses or report results that could lead to identification of any individual study participant. All participants are also given a copy of their signed consent form, which includes information about their rights under the Genetic Information Nondiscrimination Act (GINA).
6. MRI: All of the studies will be performed using an MR scanner employing pulse sequences and hardware that have been approved by the FDA for human clinical use. The field strength is 3 Tesla in all sites and all relevant operating characteristics (RF power deposition, rate of change of the field gradients, coil design) fall within the limits of FDA guidelines for NMR exposure. Participants will be carefully screened to exclude those who are pregnant or may have metal in or on their bodies that cannot be removed (e g., bullets, metal filings, body piercings, etc.). MR facility rules strictly forbid staff from entering the magnet room carrying metal objects. The risk of claustrophobia is minimized by (1) screening participants for self-reported claustrophobia, (2) scheduling an adaptation session prior to testing that provides an introduction to the testing facility and equipment and a brief acclimation session within the MR scanner; and (3) making sure the participant is lying comfortably with head and neck supported and providing ear protection, a mirror to see out, a button to signal distress, and an intercom. Scan time will be kept to a minimum and will not exceed 55 minutes. While raw data is pseudo-anonymized there is a risk that the participant's identity may be discerned by investigators through facial features and ear data. The NIMH NDA has implemented measures to protect participants' anonymity, including requiring scientists who access MRI data via the NDA to agree to not perform analyses or report results that could lead to identification of any individual study participant
7. EEG: Standard procedures will be used to clean the electrode cap after each study using a special bactericidal cleanser. In addition, the duration of electrode attachment rarely exceeds 30 minutes, minimizing the development of skin irritation. Risks of transmission of infection are minimized by washing and sterilizing the electrode caps between uses.
8. EMA / Digital Phenotyping
    a) Confidentiality: This smartphone platform in the study use up-to-date security measures that are consistent with those used by Electronic Medical Records and are HIPAA compliant. The platform has already been approved for mental health research at several US hospitals as well as in Canada, China, and Bulgaria reflecting

ability to meet and exceed requirements in different countries and settings. All data collected via these apps are encrypted on the smartphone itself and then transmitted using Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering information while it is in the transmission pipeline. In addition, all data stored within the apps is pseudo-anonymized with a unique key, again using the NIH Pseudo GUID tool. Security measures to protect privacy threats associated with users' devices include the following measures: password protection, session logs, and any data stored locally is automatically encrypted using 256-bit encryption based on the user authentication information and cannot be accessed without this information. We will clearly inform the participants of the risk of data insecurity as part of the informed consent process. We will instruct participants on how to add a PIN to their phone to prevent unwanted access. Participants will never be individually named or identifiable in any presentation. While raw geolocation data is pseudo-anonymized there is a risk that the participant's identity may be discerned by viewing their geolocation. The NIMH have implemented measures to protect participants' anonymity, including requiring scientists who request geolocation results to agree to not perform analyses or report results that could lead to identification of any individual study participant and also to obtain IRB approval to use the data.

b) Driving and Using the App: Another risk is that participants could occasionally try to take surveys on the mobile application while driving. Participants will be instructed never to use the mobile phone will driving and they will be made aware of the physical, financial, and legal risks that doing so would entail. Should the research team become aware of a participant driving while using the mobile phone, the PI and all mentors will consult as to the most appropriate way to eliminate this risk.

c) Suicidality or Psychiatric Deterioration: Suicidality is assessed in the context of standard care provided at each site. In the initial appointment participants will be informed that although study staff will review the information related to suicide and safety gathered by the app, they cannot expect that study staff will review the information in a time frame to be able to act immediately on this information. This warning will be reiterated when participants launch the mobile app along with instructions to local and national resources that participants should seek care if they experience a worsening of their condition from a health care professional, emergency room, or helpline. Site PIs will have access to all participant data and will make a determination as to how to follow-up, which may include calling the participant for further evaluation, calling the participant's local clinician, calling the on-call emergency line, calling emergency services to perform a health and safety check, or if necessary to bring the participant to the emergency department for a crisis evaluation.

d) Axivity AX: Participants will be instructed to discontinue wearing the device on their wrist if any skin irritation arises. In addition, it the participant finds that wearing the device causes any psychological distress they will be told to discontinue. The Axivity AX is an optional procedure and discontinuing its use will not have any impact on the participant's involvement in the study.

9. Face and Voice Expression / NLP. Raw audio, video, and transcript files will not be shared outside of the Yale network. Audio files will be transcribed using HIPAA-compliant services such as TranscribeMe or Zoom or similar HIPAA-compliant software, which interfaces directly with the HIPAA-compliant YaleREDCap. Pseudo-anonymized transcripts and extracted speech acoustic and face expression variables that cannot be reconstituted to identify specific individuals will be sent to the NDA.

18. RESEARCH RELATED HARM/INJURY

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

The research is considered minimal risk. All participants in the ProNET study will be able to receive medical or psychological treatment at the local site for any injury or harm that may occur.

19. POTENTIAL BENEFIT TO SUBJECTS

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

Data generated within the ProNet study may be utilized to improve the treatment offered by CHR programs in general. ProNET generated data from a specific site may also be used by that site to improve site specific treatment. Participants may benefit from these advances in treatment models. Further, clinicians will have access in real time to data about their participants which can be used to inform treatment decisions. Participants may benefit by better access by their clinicians to data that can help clinical decision making.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

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

ProNET participants will be recruited from referral sources in the community and within the site's existing health system/clinic. The site recruiter will provide their contact information to referral sources so that potential participants may reach out to the recruiter to further discuss the study. The recruiter will ensure that all communication with potential participants follows HIPAA and local site guidelines regarding phone and email communications. Data containing identifiable information located at data collection sites will be protected by site institutional policies and procedures. Data containing identifiable information located at the ProNET Secure Data Lake at Yale will be protected by Yale institutional policies and procedures including storage on HIPAA- compliant servers.

21. COSTS TO SUBJECTS

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

There is no cost for participants to participate in the ProNET study. All outcomes assessments and tests are paid for by the grant.

22. PAYMENT TO SUBJECTS

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

Participants will receive $30 per hour for completion of ProNET Assessments and $2 per visit for the EMA survey.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

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

Recruitment and consent will follow procedures that are IRB approved. Referrals for the study will come from clinicians or self-referral by participants. If a clinician referral, the clinician will first seek permission from the participant for referral. The consent process begins with an assessment of the participant's ability to give informed consent. Participants who on initial evaluation by the study investigator are deemed not to be capable of giving informed consent will not be evaluated further. Participants who are deemed capable of giving informed consent will then be provided with a full and complete description of the study. Informed consent will be obtained in a shared decision-making context and reasons for agreement or refusal will be documented.

Informed consent will be documented when the participant signs the consent form that has been approved by the Institutional Review Board.

Consent will be obtained at local site where the study is being conducted. Consent will be captured electronically using the REDCap data system. In case of problems with the electronic system consent may be obtained via paper either in person or by email, mail or fax. In case of paper remote consent, a member of the research team will review the consent form with the participant and/or parent/legal guardian over the phone or via telehealth. Participants and/or parent/legal guardian will then be asked to sign the consent form before emailing, mailing, or faxing the form back to the site. Once the study team receives the signed copy, the investigator will sign the consent form and a copy will be made and sent to the participant for his/her records.

A copy of the consent/assent will be provided to the participant and/or parent or legal guardian.

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

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

The CHR programs participating in the ProNET study allow the enrollment of adolescents into their CHR program. These participants will not be excluded from the ProNET study, as there is no anticipated additional risk for this population.
Participants under the age for providing consent for research in the site jurisdiction will have their parent or legal guardian sign an informed consent utilizing the process described above and the participant will sign an assent form. If the participant reaches the age for providing consent while in the study, re-consent from the participant will be obtained. If the participant declines to provide re-consent, further study participation will end.

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

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*

- *list the individuals from who permission will be obtained in order of priority*
- *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
- *Describe whether assent will be documented and the process to document assent*
- *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

N/A

If the study will enroll non-English speaking subjects:

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

For the US sites, we will include participants who speak English and Spanish. The ICF and all outcomes assessments will be translated to Spanish. Local sites will only enroll Spanish speaking participants if they have staff or local translators who can speak to /translate the information to Spanish for the participant. For the ex-US sites the ICF will be translated to the local language.

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

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

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

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

SUBSECTION 1

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

SUBSECTION 2

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

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25. WAIVER OF HIPAA AUTHORIZATION ☒ N/A

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

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

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

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

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

26. VULNERABLE POPULATIONS:

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

☒ *Children or viable neonate*
☐ *Cognitively impaired*
☒ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*

☐ *Prisoners*
☐ *NSLIJ Employees, residents, fellows, etc*
☒ *poor/uninsured*
☒ *Students* ☒ *Minorities*
☐ *Elderly* ☒ *Healthy Controls*

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

Individuals between the ages of 12 and 30 years old will be included in this study, because onset of clinical high-risk symptoms most often develops during adolescence or early adulthood. Minors that are enrolled into the ProNET study will require parental agreement as well as agreement by the minor as described in the consent process. The ProNET study does not directly mandate any particular treatment and sites will provide their best choice of treatment to those who are pregnant, poor, students and minorities. There is no additional risk to these vulnerable populations.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

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

The ProNET study will include 9 ex- US sites and 17 sites across the United States. All 26 sites have PIs experienced in CHR and have participated in multiple research studies in the past. Each site will employ a dedicated research coordinator and research assistant who will be trained by the ProNET team on all data collection procedures. The ProNET study has 3 lead investigators who will employ a Project Director to oversee the sites and provide regular updates to the Operations Core consisting of the lead PI's and select co-investigators. This core will meet weekly via conference call to review all aspects of project progress and performance. The proposed Operations Core central team has significant experience managing community mental health centers (CMHCs) participating in research projects with CHR participants. The Operations Core team will provide administrative support and oversight for the ProNET study, which includes oversight of recruitment and retention of participants, the data collection, problem solving barriers to ensure timely data collection.

The ProNET team Project director will be regularly monitoring the recruitment, retention, and completion of all required study procedures at each site. The Project Director will have access to the data management systems which will provide oversight of the collection of all study data. Issues identified at any site will be brought to the attention of the local site PI as well as the ProNET Operations Core. The Project Director will also be holding monthly group calls with the local site coordinators as well as individual calls to provide oversight, identify best practices, and problem solve any issues that may arise.

The ProNET Project Director will provide training to each site's coordinator on the definition and collection of unanticipated problems, including the completion and submission of the Unanticipated Problem Form to the IRB. At the monthly calls with the sites the ProNET Project Director will remind the sites about the submission of any unanticipated problems that may occur. In the event that a site does identify an unanticipated problem, the Project Director will assist the site in the completion and submission of the Unanticipated Problem Form to the IRB as well as alert the Operations Core of the event.

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

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