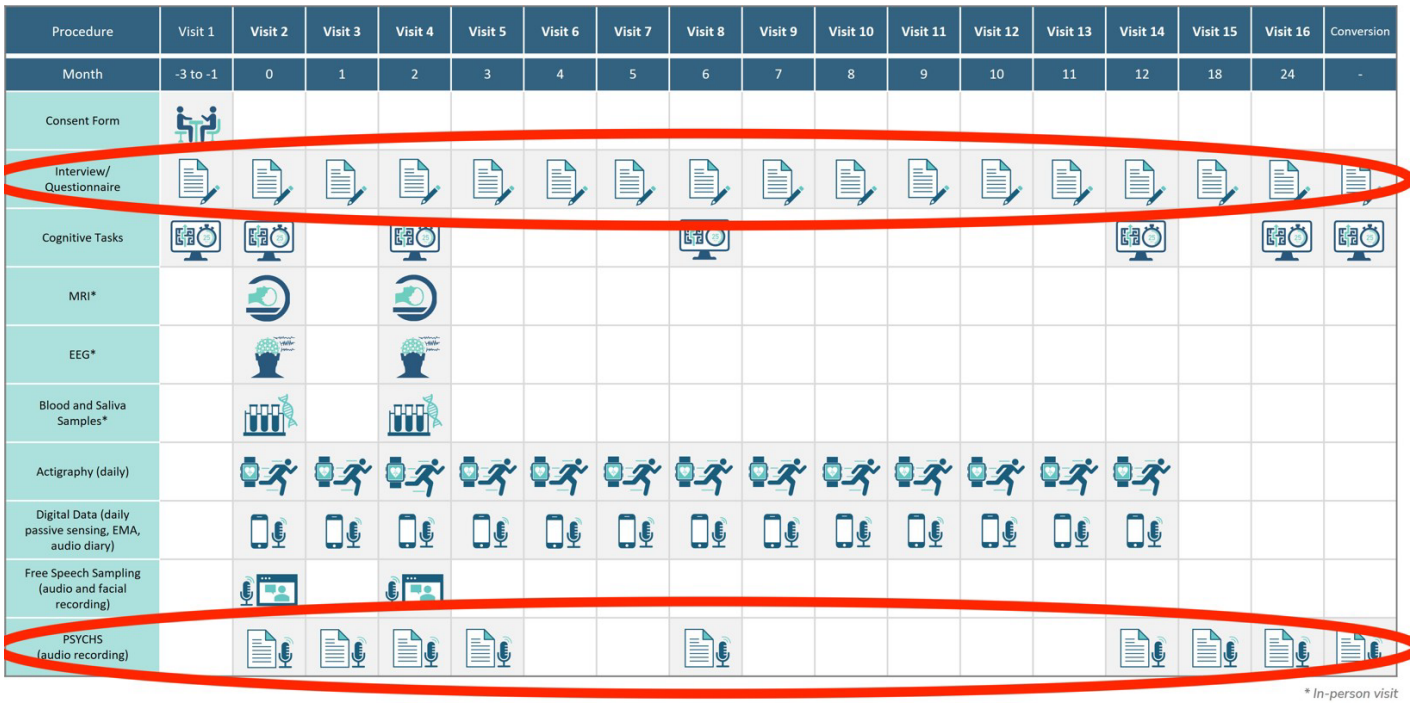
Standard Operating Procedures for Clinical Data Acquisition

Accelerating Medicines Partnership® SCHIZOPHRENIA

An observational study examining clinical trajectories and predictors of outcomes in the clinical high-risk population.

Version 9, Revised: January 23rd, 2023



Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Conversion
Month	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	18	24	-
Consent Form																	
Interview/ Questionnaire																	
Cognitive Tasks																	
MRI*																	
EEG*																	
Blood and Saliva Samples*																	
Actigraphy (daily)																	
Digital Data (daily passive sensing, EMA, audio diary)																	
Free Speech Sampling (audio and facial recording)																	
PSYCHS (audio recording)																	

** In-person visit*

1. PARTICIPANT POPULATION

1.1. Description

Clinical High Risk (CHR) participants and healthy control (HC) volunteers aged between 12-30 (inclusive).

1.2. Recruitment

Each site is well connected within their community and employs various activities to engage their referral network. Research Assistants (RAs) or site recruiters will recruit help accepting CHR patients. Activities used to recruit CHR participants may include:

- Dedicated CHR referral/intake coordinators to assist new referrals from initial contact to evaluation and enrollment.
- Reviewing medical records of new referrals and those on waitlists.
- Consulting with clinicians working in the recruiting clinics.
- Sitting in on clinical review at the respective recruitment sites.
- 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, newsletters, and social media.
- 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, radio, and newspaper ads).

If a participant is engaged in treatment, the researcher will contact the relevant clinician to advise before approaching the client. Pre-screening questions can be completed via phone call to determine the client's appropriateness for the study. Notes will be recorded in the relevant clinical record outlining the content of the phone call and the outcome of the pre-screening call. The participant will be recorded on the pre-screening log.

These recruitment methods closely align with other studies recruiting this clinical population. Initial suitability will be established by the fact that the young person is presenting with CHR criteria, falls within the targeted age range, appears competent to consent to the study, and there are no obvious indications that they meet exclusion criteria. The healthy control cohort will be recruited from the community using a variety of methods including social media posts and word of mouth as well as from an already existing list of HC volunteers who have indicated they are open to hearing about new research participation opportunities. A de-identified log of patients and HC volunteers who are considered for but not enrolled in the study and the reasons for exclusion/refusal will be retained by the study team.

1.3. Inclusion/Exclusion Criteria

Only participants who meet all the inclusion and none of the exclusion criteria will be eligible to participate in the study.

CHR:

Inclusion	
1	Understand and sign informed consent for all procedures if eligible
2	Individuals between 12 and 30 years old

3	Meet diagnostic criteria for CHR as assessed with the PSYCHS including any one of the following (*Attenuated Positive Symptom Syndrome/APSS, Brief Intermittent Psychotic Syndrome/BLIPS, or Genetic Risk and Deterioration Syndrome/GRD) from the SIPS or Attenuated Positive Symptom Syndrome/APSS, Brief and Limited Intermittent Psychotic Symptoms/BLIPS, or Genetic Risk and Deterioration Syndrome/GRD) for both) as assessed by the PSYCHS* from the SIPS or CAARMS or both
Exclusion	
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) If potential participants are on antipsychotic medication at the time of study screening, they can be titrated off this medication prior to study enrollment;
2	Documented history of intellectual disability
3	Past or current clinically relevant central nervous system disorder. When necessary, RAs 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 (Positive Symptoms CAARMS Harmonized with SIPS) criteria.

Healthy Controls:

Healthy control volunteers must meet CHR participant inclusion criteria 1-2. They must not (1) meet criteria for any CHR psychosis-risk syndrome, any current or past psychotic disorder or Cluster A personality disorder diagnosis; (2) be receiving any current treatment with psychotropic medication; or (3) have a family history (in first-degree relatives) of psychotic spectrum disorders or (4) meet CHR exclusion criteria 2-3. Healthy controls will be matched to CHR participants on age, sex, and SES.

Both ProNET and PRESCIENT teams will complete Quality Control (QC) procedures to confirm that participants meet inclusion/exclusion criteria as outlined in the Network Monitoring Plan.

1.3.1. Antipsychotic Dose Equivalents

The doses provided in the table below are currently equivalent to a cumulative 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.

Abbreviated Drug Name, Drug Name and Trade name		Dose in mg
AMS	Amisulpride (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	Sulpride (Dolmatil, Sulpitil, Sulparex)	5000
THI	Thiothixine (Navane)	100
THZ	Thioridizine (Melleril, Aldazine)	2500
TPZ	Trifluoperazine (Stelazine)	125
ZPD	Ziprasidone (Geodon)	1500

2. ASCERTAINMENT AND OUTCOME SCHEDULE OF ASSESSMENTS / INSTRUMENTS

Visit	**Visit 1**	**Visit 2**	**Visits 3, 5**	**Visits 4, 8, 15**	**Visits 14, 16**
Month	Month -1	Month 0	Month 1, 3	Month 2, 6, 18	Month 12, 24
Informed consent	30				
Inclusion/exclusion criteria review					
Past/current meds, Psychosocial Treatment, Adverse Events	15	5	5	5	5
Sociodemographics		5			
FIGS	15				
Health Conditions (Medical History/Psychiatric History)	5				
Structured Clinical Interview for DSM-5 Personality (SCID-dPQ))	15				
Structured Clinical Interview for DSM-5 (SCID) (Psychosis, Mood, Substance Use)		60			45
Traumatic Brain Injury (TBI) Screening	5				
Positive Symptoms CAARMS Harmonized with SIPS (PSYCHS)	120	45	45	45	45
The Social and Occupational Functioning Scale (SOFAS)	10		5	5	5
Premorbid Adjustment Scale (PAS)			15		
Perceived Discrimination		2			
Puberty Development Scale (PDS)		3			
Negative Symptom Inventory-Psychosis Risk		20	20	20	20
Calgary Depression Scale for Schizophrenia (CDSS)		10	10	10	10

Overall Anxiety Severity & Impairment Scale (OASIS)		5	5	5	5
The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)		5		5	5
Columbia-Suicide Severity Rating Scale (C-SSRS)		5		5	5
Perceived Stress Scale (PSS)		5	5	5	5
Global functioning: Social and Role		15	15	15	15
8 - item PROMIS for sleep		5		5	5
Brief Psychiatric Rating Scale (BPRS)*		10	10	10	10
The Patient Global Impression Scale - Severity (PGI-S)		1	1	1	1
Psychosis Polyrisk Score (PPS)	10				
TOTAL TIME TO DATE (minutes)	**225**	**200**	**135**	**135**	**180**

**In addition, the BPRS (30mins) will be assessed at months 4, 5, 7, 8, 9, 10, and 11 and in the case of conversion to psychosis we will complete a conversion assessment which includes the assessments listed in visits 14 and 16 above. Other components (e.g., MRI, EEG etc.) are detailed in their respective summaries/SOPs.*

3. INSTRUMENT ADMINISTRATION

3.1. General Procedures

The Research Assistant will arrange a time to meet with the participant (and parent/guardian if the participant is a minor) to carry out the consent process. Following this, they will meet with the participant to conduct the screening and baseline assessments (visits 1 and 2). Assessments may be split across multiple visits if this is preferred by the participant or the participant and their parent/legal guardian. All assessments/instruments above can be completed in person or via video call (see section 6 for details on remote assessments). The RA will complete all screening assessments (visit 1) prior to completing baseline (visit 2) assessments. If the participant meets eligibility criteria after screening the RA may proceed to the baseline assessment. Baseline procedures can begin on the same day of screening as long as the participant is deemed to be eligible after completing the screening assessments.

For most of the measures, ratings will be entered directly into the RPMS/REDCap during the visit. For measures that require notetaking and consideration prior to making a rating, the following procedures will be followed:

3.1.1. PRESCIENT

Except for measures that will be directly entered into RPMS, the RA will download the measure as a PDF onto a writable iPad. During the visit, they will take notes electronically using a stylus pen and make their ratings within two days of the visit following the visit. All PDF forms with original notes will be saved and uploaded into the RPMS and the RA will enter their ratings into the RPMS data entry forms. A back-up paper source document will be available for emergency use should the RA be unable to use the writeable PDFs, but this will be the exception. Should this happen then the paper source document should be scanned and uploaded.

3.1.2. ProNET

During the visit, the RA or clinical rater will enter their notes into a free-text box for the measure in REDCap. These notes will be saved in the REDCap form and the RA or clinical rater will later review the notes to make their ratings. The ratings will then be entered into the appropriate fields in the REDCap form. Ratings should be entered into the form within 1 day of the clinical rating, except for the PSYCHS which may require consultation on the weekly consensus call and then will be entered or edited immediately following the call.

3.2. Sociodemographics

Demographics will include age, sex, gender, race, ethnicity, socioeconomic status, employment, educational attainment and age and education of biological parents. The demographics will also ask whether the participant has a biological sibling participating in the study.

3.3. Medical/Psychiatric History

RAs will collect medical and psychiatric history via participant interview and review of medical records if available.

3.4. Traumatic Brain Injury Screening

If during the medical and psychiatric history, it is reported that a participant has had a prior brain injury the Traumatic Brain Injury Screening instrument will be completed.

3.5. Past/current medications, psychosocial treatments, 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 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.

3.6. Schizotypal Personality (SCID-5 PQ)

The SCID-5 PQ is a semi-structured interview for DSM-5 and will be used to assess diagnostic criteria for Schizotypal Personality Disorder.

3.7. Structured Clinical Interview for DSM-5 (SCID) (Psychosis, Mood, Substance Use)

The SCID is a semi-structured interview for DSM-5 and will be used to assess diagnostic criteria for the psychosis, substance use, and mood modules.

3.8. Family History Index FIGS

The FIGS will be administered to check whether the participant has a first degree relative with a psychotic disorder along with the SOFAS to determine whether the participant meets CHR vulnerability per the CAARMS or Genetic risk and deterioration per the SIPS.

3.9. Positive Symptoms CAARMS Harmonized with SIPS (PSYCHS)

This harmonized version of the CAARMS and SIPS (positive symptom items only) will be administered. Positive symptom ratings that determine the presence, frequency, and severity of the CAARMS P1-P4 and SIPS P1-P5 will determine whether the participant meets one of the required CHR criteria for the study and to determine their clinical CHR state at subsequent follow-ups.

With the consent of the participant, the PSYCHS portion of the visit will be audio 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. Notes will be typed directly into REDCap for ProNET and notes will be uploaded as a PDF for PRESCIENT.

3.10. Social and Occupational Functioning Assessment Scale (SOFAS)

The SOFAS will be used to determine social and occupational functioning at baseline and follow up time points. The baseline ratings will be used to determine eligibility for the CHR vulnerability group or the Genetic Risk and Deterioration group along with the FIGS.

- If a healthy control participant does not have any current/past mental health problems, then you use their current SOFAS rating as their premorbid SOFAS.
- If a healthy control does have current/past mental health problems (for example, depression), then then you use their premorbid SOFAS. Ask about their level of social and

occupational functioning before they developed their symptoms.
- Likewise, for a CHR participant if they had past mental health problems that preceded their CHR symptoms you would ask about functioning before they developed their symptoms.

3.11. Premorbid Adjustment Scale (PAS)

The PAS will be used to assess premorbid functioning across developmental periods and across several domains. Each domain is rated on a 0-to-6-point scale, with 0 indicating normal adjustment and 6 indicating severe impairment. The "premorbid" period for PAS purposes is the period ending six months prior to the participant first meeting CHR criteria.

3.12. Perceived Discrimination Scale

The Perceived Discrimination Scale self-report will be used to examine whether perceived discrimination is a predictive factor for transition to psychosis.

3.13. Pubertal Development Scale (PDS)

The self-report Pubertal Development Scale (PDS) will be used to assess physical changes during puberty.

3.14. Negative Symptom Inventory-Psychosis Risk (NSI-PR)

Negative symptoms will be assessed utilizing 11 items from the Negative Symptom Inventory-Psychosis Risk which assess the 5 NIMH consensus domains (anhedonia, avolition, asociality, alogia, blunted affect)

3.15. Calgary Depression Scale for Schizophrenia (CDSS)

Depression will be assessed utilizing the Calgary Depression Scale for Schizophrenia (CDSS)

3.16. Overall Anxiety Severity and Impairment Scale (OASIS)

The self-report Overall Anxiety Severity and Impairment Scale (OASIS) will be used for anxiety severity.

3.17. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

Substance use will be evaluated using the self-report Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).

3.18. Perceived Stress Scale (PSS)

The PSS is a self-report 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.

3.19. Global functioning: Social and Role

Functioning will be assessed utilizing the Global Functioning: Social and Role scales that were developed specifically for CHR.

3.20. 8 - item PROMIS for sleep

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.

3.21. Brief Psychiatric Rating Scale (BPRS)

General psychopathology will be assessed utilizing the Brief Psychiatric Rating Scale (BPRS)

3.22. The Patient Global Impression Scale - Severity (PGI-S)

The Patient Global Impression Scale - Severity (PGI-S) will be utilized to assess patient reported impression of severity of illness.

3.23. Psychosis Polyrisk Score (PPS)

The PPS is a self-report measure used to assess known environmental risk factors for psychosis.

3.24. Columbia Suicide Severity Rating Scale (CSSRS)

The CSSRS will be used to assess suicidal ideation and history of suicide attempts.

3.25. Quality Control of Clinical Data

The data collection team at both ProNET and PRESCIENT will monitor the collection of data at all data points. Reasons for missing data will be reviewed and discussed with sites. Monitoring of data within and across data collection forms, i.e., cross checking measures, will be the responsibility of the DPACC. The QC procedures completed by the DPACC will be developed and documented in an additional QC document.

One important exception is the QC for the PSYCHS, which is partly conducted by the Research Networks. As described in section 4.3, the Research Networks will conduct the Consensus Calls. When systematic errors are noticed during these calls (within 1 specific symptom) and/or too many errors are made (across the scale), the transcripts of the interviews can be used for a cross check with the scores as entered into RPMS/Redcap. These transcripts are applied as a tool for further investigation and to obtain insight into what the underlying problem is for the incorrect scoring if this cannot be gained from the discussion during the consensus call.

A cross check between the transcript and the scores as entered in RPMS/RedCAP are indicated in the following cases:

- A deviation of 2 or more points on a symptom, and the underlying problem cannot be understood and resolved during the consensus call.
- Repeated deviations of 1 point on a specific symptom across the rater group or within 1 rater - this would suggest a systematic issue and may warrant further investigation.
- A faulty conclusion/diagnosis of 'CHR' (at screening) or 'transition' (during the study), which cannot be understood and resolved based on the info provided by the rater during the consensus call.

If these 3 points do not lead to the need to cross check transcripts with scores, a sample of 2.5 % should be drawn (including at least 1 assessment of each site) to cross check. In case more than 1 assessment is checked for an individual site, an assessment of another rater will be selected. These checks are performed by four current experts on the PSYCHS: Scott Woods, Alison Yung, Melissa Kerr and Barbara Walsh.

4. TRAINING AND SUPPORT

4.1. Staff Qualifications

All staff involved in recruitment and assessment of research participants will have appropriate training in recruitment and assessment procedures. They will also complete a Good Clinical Practice (GCP) training course that meets local IRB requirements. Training procedures are detailed below.

4.2. Training Procedures

PRESCIENT and ProNET have discussed the implementation of training across the two networks. Training on all measures will be combined across the networks to ensure consistency of administration and ratings. Each network will be responsible for ensuring that staff sign up for the necessary training, complete all aspects of that training and are competent to carry out study

procedures and assessments. They will ensure that appropriate support and additional training is provided in an ongoing way throughout the study. Experienced trainers have been allocated to the various measures to ensure accurate and consistent administration and scoring.

Outcome measures in ProNET and PRESCIENT include clinical interviews, self-reports in which the rater asks the questions and self-reports that are completed by the participant. Training will occur for all clinical measures and all raters will be required to have certificates of training for all measures for which they will be responsible. This will ensure that they have completed the necessary training and met acceptable reliability on each of the measures. Documentation of certification on each measure that requires certification will be recorded by the coordinators for each Network and only certified raters will be allowed to conduct the necessary assessments. Each site will not be activated to start recruitment until there is at least 1 certified rater for each assessment.

At each site there will be at least one senior clinician who will be responsible for (i) overseeing that all raters complete their training, (ii) being a resource to clinical raters with respect to scoring and rating and also for managing participant responses that need further review and (iii) ensuring that all new raters who join the projects at a later date complete the required training. The senior clinician will ensure that all raters have some familiarity with the measures either by reviewing them or observing more senior or trained raters prior to the official training. The senior clinician will lead the rater training activities at each site as outlined in the training plan for each measure described in the sections below.

All training sessions will be completed virtually, repeated at least twice to ensure raters from different time zones can attend and recorded for later use. Recorded sessions and all slides presented by trainers during the training session will be available immediately after in a library of resources. Initial training for all measures will occur prior to the startup of ProNET and PRESCIENT. All training procedures must be followed by all new raters who join either of the projects later. To ensure consistency in training across both networks, raters from both networks will be trained together.

4.2.1. PSYCHS criteria

Key trainers will be Dr. Barbara Walsh and Melissa Kerr. Drs Woods, Yung, and Addington helped with the development of the training. Dr Alison Yung and Dr Scott Woods are the developers of the SIPS and CAARMS. Drs Woods, Yung, Walsh, Kerr and Dr Sophie Parker from the UK developed the new instrument PSYCHS.

1. Prior to the training session, all raters will receive a copy of the PSYCHS. All raters will be asked to familiarize themselves with the new format of the measures prior to the training. This should involve discussion with senior clinicians so that raters are well prepared for the training.
2. There will be 2 formal training sessions, one for 2 hours and one for 3 hours (split into two parts) that all raters will be required to attend (virtually). The training will include a complete review of the PSYCHS, highlighting salient features of the updated measures and differences between the PSYCHS and the CAARMS and SIPS. The trainers will specifically target each of the attenuated psychotic symptoms and explain the rationale for the updated anchors and scoring conventions.
3. After the training session all raters will be required to practice either live or mock interviews under the supervision of the senior clinician until that supervisor feels they are ready to begin the certification process. Raters will then rate 3 mock interviews specifically developed for ProNET and PRESCIENT.
4. Raters will be considered reliable if (i) all scores on all 15 individual attenuated psychotic symptoms are within one point of the established gold standard, (ii) the total score of all 15

symptoms on the PSYCHS is within 80% of the established gold standard, (iii) all scores fall in the appropriate ranges, i.e., 0-2 is normal, 3-5 CHR and 6 psychotic, and for all three cases the rater diagnosis matches the gold standard diagnosis (CHR vs psychotic vs neither). This standard will be met on all three mock interviews. Raters who do not meet the target will be required to do additional interviews with their senior clinician until they meet this target with their supervisor and then can repeat the certification interviews.

4.2.2. Structured Clinical Interview for DSM-5

Training will be conducted by Dr. Monica Calkins of the University of Pennsylvania, one of the ProNET investigators. This training will be in the format of "train the trainer." Attendees will be senior clinicians at each site, with extensive SCID experience, who will be responsible for SCID training for all raters at their respective sites. Clinical raters can attend if they choose.

1. Prior to the train-the-trainer session, all raters will be asked to review the SCID manual for the psychosis, mood and substance use modules and the module for schizotypy.
2. There will be a 2-hour formal training session that all senior clinicians will be required to attend (virtually). The training includes an in-depth overview of the SCID modules, discussion of procedures for rating each module and detailed standard recommended training protocols. Q & A will occur during training. Slides presented in the training will be available. Once this training is completed, the senior clinicians can start training raters at their site.
3. Onsite training:
    a. Senior clinicians will train raters at their respective sites (approximately 5 hours). Training templates are provided for use at each site. Additional training materials can be provided if needed. Raters should complete observations of SCID interviews conducted at their site and conduct supervised mock or actual sessions of the required modules. When the senior clinician deems a rater as "certifiable" based on the Certification Checklist (a detailed 54 item check list of SCID rater skills), the local senior clinician will submit ratings on the checklist via a Google Form. Penn will score checklist and respond to clinician with the score. Rater must achieve >=85% on the checklist. Senior clinicians will work with site raters until they demonstrate the required skills to achieve at least 85%.
    b. Senior clinician and raters will view a video recording of a mock SCID interview. They will submit to Dr. Calkins at Penn independent ratings and diagnoses.
4. Reliability will be calculated in relation to the established gold standard video (mentioned in Step 3b) and ratings for each rater at each site via Cronbach's alpha calculated across all items on the scale. Trainers/trainees will submit ratings via a google form and Penn will calculate reliability ratings. Intraclass correlations (ICC) target for ratings on the video is >=0.75 (excellent range) with gold standard ratings. A report of results will be returned to the senior clinician. Raters who do not meet the gold standard will be required to perform additional SCID practice under the supervision of the site senior clinician as well as to redo the video ratings.

4.2.3. Negative Symptom Inventory-Psychosis Risk (NSI-PR)

Training will be conducted by Dr. Greg Strauss of the University of Georgia, a ProNET investigator. Dr Strauss is the developer of the NSI-PR and has many years' experience training on negative symptoms for a wide range of trials including pharmacological randomized control trials (RCT).

1. Prior to the training session, all raters will be asked to review the NSI-PR manual, interview guide, scoresheet, and frequently-asked-questions document prior to training.
2. There will be a 2-hour formal training session that all raters will be required to attend (virtually). The training includes an in-depth overview of the measure, discussion of procedures for rating each item, and example videos displaying varying levels of blunted facial and vocal affect. Q & A will occur during training.

3. After the training session, raters under the supervision of the site senior clinician should practice administering the NSI-PR so that they are familiar with it. They will then be required to watch a 1-hour training video which has examples of 3 cases of varying degrees of severity. Raters will rate those cases and then under the supervision of the senior clinician consult the established gold standard rating guide that has explanations for the gold standard rating for each case. If their ratings are more than 1 point off from the gold standard, they are to consult with the senior clinician at their site, who will advise on where they need additional help. Ratings on the three cases will be submitted to Dr. Strauss.
4. Reliability will be calculated in relation to the gold standard video and ratings for each rater at each site via Cronbach's alpha calculated across all items on the scale. Raters will be required to meet a reliability threshold of >=0.80 on the total score and all individual scores must be within one point of the gold standard. Raters who do not meet this standard will be required to either review scores or rate an additional video or have retraining depending on how much their scores are off from the gold standard.

4.2.4. Global functioning: Social and Role (GF:S, GF:R)

Training will be conducted by Dr. Andrea Auther of Zucker Hillside Hospital, New York. Dr. Auther, a co-investigator on ProNET and Dr. Cornblatt, a ProNET Investigator, are the developers of the GF:S and the GF:R. They have many years' experience training on this measure for large consortiums, and a wide range of trials including pharmacological RCTs.

1. Prior to the training session, all raters will be asked to carefully review the questions and anchors for the GF:S and the GR:R.
2. There will be a 1.5-hour formal training session that all raters will be required to attend (virtually). The training includes an in-depth overview of the measure, and discussion of procedures for rating each scale. Q & A will occur during training.
3. After the training session, raters should practice giving at least 3 GF:S and GF:R interviews while being observed by an experienced rater or the senior clinician. Ratings should be discussed with the senior clinician. Raters will then be provided with the transcripts of three cases which they must review and provide scores for each vignette. Ratings will be returned to Dr Auther at Hillside.
4. Reliability will be calculated in relation to the gold standard. On each score raters will be required to meet a reliability threshold of >=0.80 and all scores within one point of the established gold standard. Raters who do not meet this standard will be required to either review scores, rate additional vignettes, or have retraining depending on how many scores are off.

4.2.5. Calgary Depression Scale (CDSS)

Training will be conducted by Dr. Jean Addington of the University of Calgary, a ProNET investigator and Team B/I lead. Dr. Addington is one of the developers of the CDSS and has many years' experience training in this measure for large consortiums, and a wide range of trials including pharmacological RCTs.

1. Prior to the training session, all raters will be asked to carefully review the questions and anchors for the CDSS. They will be able to observe a video of the interview.
2. There will be a 1-hour formal training session that all raters will be required to attend (virtually). The training includes an in-depth overview of the measure, and discussion of anchors for rating the scale. Q & A will occur during training.
3. After the training session, raters should practice giving at least 2 CDSS interviews while being observed by an experienced rater or the senior clinician. Ratings should be discussed with the senior clinician. Raters will then be provided with a video which they must review and then provide ratings. Ratings will be returned to Dr. Addington at Calgary.
4. Reliability will be calculated in relation to the established gold standard. Raters will be required to meet a reliability threshold of >=0.80 on the total score and all individual scores must be within one point of the gold standard. Raters who do not meet this standard will be

required to either review scores, rate an additional video, or have retraining depending on how much their scores are off from the gold standard.

4.2.6. Brief Psychiatric Rating Scale (BPRS)

Training will be conducted by Melissa Kerr of Orygen, the PRESCIENT Project Manager.

1. Prior to the training session, all raters will be asked to carefully review the questions and anchors for the BPRS. They will also receive a "handy hints" document for review.
2. There will be a 1.5-hour formal training session that all raters will be required to attend (virtually). The training includes an overview of the measure, a discussion of procedures and tips for rating the scale. A webinar role play of the BPRS will be demonstrated; raters will be asked to rate the measure during the role play and following this the webinar will go through the suggested ratings for each subscale.
3. After the training session, raters will send their ratings to M. Kerr and if the scores have drifted too far from the established gold standard ratings, they will need to contact M. Kerr to discuss the measure further or to initiate re-training.

4.2.7. Columbia-Suicide Severity rating Scale (C-SSRS)

All raters will complete the online training for the C-SSRS which is provided free by the Columbia Lighthouse Project and which provides proof of training. The Policy established by the Columbia Lighthouse Project is that the training certificate is valid for the duration of an ongoing trial where the scale is administered continuously. We therefore require training certificates to be completed ASAP for all raters which means that we will not have to monitor re-certification. Training certificates should be submitted to Susan Ray for ProNET or Melissa Kerr for PRESCIENT.

4.2.8. Remaining Measures (Self Report) to be covered in a 1- hour additional training session.

Training will be conducted by Dr. Jean Addington, Dr. Scott Woods and Melissa Kerr.

1. Prior to the training session all senior clinicians and available raters will complete themselves the following measures: Demographics, Premorbid Adjustment Scale, Childhood Trauma Questionnaire, Perceived Discrimination, Puberty Development Scale, Polyenvironmental Psychosis Risk Score, Overall Anxiety Severity & Impairment Scale, ASSIST for substance use, Perceived Stress Scale, PROMIS for sleep, Patient Global Impression of Severity, and Past/Current Meds, Psychosocial Treatment and Adverse Events. They will prepare a list of questions they might have on the administration of all these measures.
2. A detailed explanation of how to complete the Patient Global Impression of Severity, and Past/Current Meds, and Psychosocial Treatment and Adverse Events measure will be given by M. Kerr and Dr. Woods.
3. There will then be time for senior clinicians to ask any questions they may have on the self-report measures with Dr Addington.

4.3. Consensus Diagnostic Calls

Sites across the entire AMP SCZ network have been split into five groups according to time zone with sites from both networks represented in the European group and the Australia/Asia group. Each group will be led by an investigator with extensive experience in training and administration of the SIPS and/or CAARMS. Group leaders will be supported by 1-2 co-leads.

All staff involved in completing the PSYCHS for ascertainment will attend regular zoom calls to determine by consensus that participants meet entry criteria. Prior to each call a standard vignette will be circulated to the group in which the site is participating. Each vignette, which will report on inclusion and exclusion criteria and describe all measurement concepts for the PSYCHS ratings, will be reviewed so that consensus on meeting criteria is made for every participant included. The expectation is that senior clinicians at each site will have reviewed the vignette prior to submission to the consensus group.

When a participant is thought to have made the transition to psychosis, a vignetted detailing the transition will also be prepared and the above procedure for consensus will also be followed.

4.4 Ongoing Reliability Training

Ongoing reliability will occur for the PSYCHS. Raters, whose PSYCHS certification is more than 6 months old, will be expected to renew their certification on an annual basis (Fall 2023, Fall 2024.) Raters will rate one mock interview specifically developed for ProNET and PRESCIENT.

Raters will be considered reliable if (i) all scores on all 15 individual attenuated psychotic symptoms are within one point of the established gold standard, (ii) the total score of all 15 symptoms on the PSYCHS is within 80% of the established gold standard, (iii) all scores fall in the appropriate ranges, i.e., 0-2 is normal, 3-5 CHR and 6 psychotic, and the rater diagnosis matches the gold standard diagnosis (CHR vs psychotic vs neither). Raters who do not meet the target will be required to do additional interviews with their senior clinician until they meet this target with their supervisor and then can repeat the certification interviews.

For other key measures original trainers will distribute material for all raters to review following the schedule below.

Measure	Person	Dates
PSYCHS	M. Kerr & B. Walsh	Sept-Oct 2023, Sept-Oct 2024
CDSS	J. Addington	November 2023, November 2024
Global functioning: Social & Role	A. Auther	January 2024, January 2025
NSI-PR	G. Strauss	February 2024, February 2025
SCID	M. Calkins	March 2024, March 2025
BPRS	M. Kerr	April 2024, April 2025

5. WORKING REMOTELY

Due to limitations such as Covid-19 or difficulty for participants to attend, it may be necessary at times during the study for recruitment, consent, and assessments to be completed remotely. If this occurs, video and phone systems at the relevant research organization or site should be used. General procedures are outlined below.

5.1. Booking Appointments

RAs will contact the participant to book in a video call or phone call and provide instructions on how to access the call. The participant will be advised to find a quiet space with access to a charger for their device and a strong and stable internet connection.

When scheduling a participant's appointment, the RA should send a calendar invite to the relevant site Principal Investigator (PI) or their designee. This will alert the team to ensure they are available to standby in case of duress during the assessment.

5.2. Conducting Assessments

Screening and clinical interviews can be done over videocall or phone. RAs will use their judgement to determine the best mode of communication and will advise the young person of the length of the appointment prior to the visit.

Notes outlining the content of the session and any concerns which arose will be documented on the relevant clinical record.

6. ABBREVIATIONS

ABBREVIATION	TERM IN FULL
APS	Attenuated Psychotic Symptoms
CAARMS	Comprehensive Assessment of At Risk Mental States
CHR	Clinical High Risk for psychosis
CSSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual for Psychiatric Disorders – Fifth Edition
GCP	Good Clinical Practice
FIGS	Family Interview for Genetics Studies
HC	Healthy Control
PAS	Premorbid Functioning Scale
PI	Principal Investigator
PID-5	Personality Inventory for DSM-5
PSYCHS	Positive Symptoms CAARMS Harmonized with SIPS
RA	Research Assistant
REDCap	Research Electronic Data Capture
RPMS	Research Project Management System
SCID-5	Structured Clinical Interview for DSM-5
SIPS	Structured Interview for Prodromal Syndromes
SOFAS	Social and Occupational Functioning Scale
SOP	Standard Operating Procedure

7. SOURCES

Dose equivalents for amisulpride, aripiprazole, chlorpromazine, clozapine, droperidol, fluphenazine, haloperidol, olanzapine, pericyazine, pimozide, perphenazine, quetiapine, risperidone, sulpride, thiothixine, thioridizine, trifluoperazine, and ziprasidone taken from Andreasen et al., Biol Psychiatr 2010;67:255-262. Asenapine, brexpiprazole, cariprazine, and iloperidone are taken from the primary estimate of minimum effective dose in Table 1 or text of Takeuchi et al, Schizophr Bull 2020;46:1439-1458. Lurasidone=ziprasidone and paliperidone-risperidone per Takeuchi. Lumateperone is taken from effectiveness of a single dose studied (42 mg).

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