Cover Page - AMP SCZ® Observational Study

Accelerating Medicines Partnership® Schizophrenia Observational Study

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Content:

Study Protocol for Trajectories and Predictors in the Clinical High Risk for Psychosis Population: Prediction Scientific Global Consortium (PRESCIENT).

STUDY PROTOCOL

Trajectories and Predictors in the Clinical High Risk for Psychosis Population: Prediction Scientific Global Consortium (PRESCIENT)

Protocol Number:	HREC 2021. 166

Sponsor:	**ORYGEN** 35 Poplar Road, Parkville, VIC, 3052 AUSTRALIA
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Version:	2.0
Version Date:	Wednesday, 17 November 2021

INVESTIGATOR SIGNATURE AND PROTOCOL AGREEMENT:

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol, Good Clinical Practice, the Declaration of Helsinki, and all applicable laws and regulations.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study participants.
This study may be terminated by Orygen with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will ensure that the requirements of the Human Research Ethics Committee (HREC) review and approval are met. I will provide Orygen with any material which is provided to the HREC for Ethical approval.
I agree to promptly report to the HREC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without HREC approval, except where necessary to ensure the safety of study participants.

I commit to involving young people at different levels in the development, conduct and communication of the study in a meaningful way, and providing sufficient support to study participants.

I agree to maintain adequate and accurate records, and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

Sponsor Representative

John Moran	Chief Operating Officer	_____	_____
Name	*Title*	*Signature*	*Date (dd/mmm/yyyy)*

Coordinating Principal Investigator

Barnaby Nelson	Professor	_____	_____
Name	*Title*	*Signature*	*Date (dd/mmm/yyyy)*

Principal Investigator – Site Specific

_[enter site PI]	*_[enter site PI title]*		
_____	_____	_____	_____
Name	*Title*	*Signature*	*Date (dd/mmm/yyyy)*

DOCUMENT HISTORY

Version	Date	Summary of change
1.0	23/Jul/2021	Original
2.0	17/Nov/2021	1. Replacement of CAARMS and SIPS measures with the Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS) measure. 2. Removal of the Trauma and Distress Scale (TADS). 3. Data transfer changes: The data collected across the PRESCIENT network will be transferred from Orygen (the network hub) directly to the NIMH NDA. 4. Raw (unprocessed) geolocation data from the digital momentary assessments will be included in the data transfer to the NIMH NDA. 5. Digital momentary assessments will now also be completed in the healthy control sample. 6. The healthy control sample in the Melbourne site has been increased from 15 to 100 (increasing the total healthy control sample from 165 to 250 participants). 7. The audiotaping of the PSYCHS interview: a) will be conducted at all follow up time points, not just at screening and month 2, b) it will no longer be an optional component. 8. The Perth recruitment site has been replaced with a recruitment site at University of Cologne, represented by the University Hospital of Cologne (UHC), Germany. 9. The laboratories for blood and saliva sample analysis have been replaced with a statement that the specific laboratories for these analyses are yet to be determined. 10. The Psychosis Polyrisk Score (PPS) will be conducted at baseline (visit 2) instead of 1 month (visit 3) in order to ensure full harmonisation with the ProNET Research Network. 11. The Penn Computerised Neurocognitive Battery (PennCNB) will be conducted at week 8 (visit 4, month 2) instead of week 12 (visit 5, month 3). This was a typological error on page 47 of the original protocol submission.

1. Table of Contents

1.1.Tables and Figures

2. Study and Sponsor Contacts

Full lists of sponsor representatives, investigators and project managers maintained within Sponsor Contact List and the Study Contact Lists.

	Contact details
Sponsor Contacts	**John Moran** Orygen 35 Poplar Road Parkville, Victoria 3052 Australia + 61 3 9966 9100 john.moran@orygen.org.au
Coordinating Principal Investigator	**Barnaby Nelson** Orygen 35 Poplar Road Parkville, Victoria 3052 Australia + 61 3 9966 9100 barnaby.nelson@orygen.org.au

3. List of Abbreviations

Abbreviation	Term in Full
AE	Adverse Event
AEPCC	Australian Early Psychosis Collaborative Consortium
AEPRN	Australian Early Psychosis Research Network
AMC	Academic Medical Centre
ANOVA	Analysis of Variance
AQ	Autism Spectrum Quotient
AQoL-4D	Assessment of Quality of Life
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUC	Area Under the Curve
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BOLD	Blood-Oxygen Level Dependent Imaging
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At Risk Mental States
CC	Clinical Control
CHR	Clinical High Risk for psychosis*
CMI	Client Management Interface
CNP	Center for Psychiatric Neuroscience
CORE	Copenhagen Research Center for Mental Health
CR	Clinical Registry
CRF	Case Report Form
CS	Clinically Significant
CTTN	Clinical Trial and Translation Network
CYMHCTN	Child and Youth Mental Health Clinical Trial Network
DPACC	Data Processing, Analysis and Coordination Center
DSM-5	Diagnostic and Statistical Manual for Psychiatric Disorders – Fifth Edition
DSMC	Data Safety Monitoring Committee
DUP	Duration of Untreated Psychosis
EASY	Early Assessment Service for Young people with psychosis
eCRF	electronic Case Report Form
EEG	Electroencephalography
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	Ecological Momentary Assessment
EPIP	Early Psychosis Intervention Programme
EU	European Union

Abbreviation	Term in Full
FEP	First Episode Psychosis
FPFV	First Patient First Visit
FSIQ	Full Scale Intelligence Quotient
GAD-7	Generalized Anxiety Disorder 7-item
GCP	Good Clinical Practice
GETIT	Gwangju Early Treatment & Intervention Team
GUID	Globally Unique Identifier
GWAS	Genome-Wide Association Studies
HC	Healthy Control
HREC	Human Research Ethics Committee or local equivalent Independent Review Board (IRB) or Institutional Ethics Committee (IEC)
HEP	headspace Early Psychosis programs
ICH	International Conference on Harmonisation
IPASE	Inventory of Psychotic-Like Anomalous Self-Experiences
IQ	Intelligence Quotient
K-10	Kessler Psychological Distress Scale
LPLV	Last Patient Last Visit
MMN	Mismatch Negativity
MUFA	Monounsaturated Fatty Acids
NCS	Not Clinically Significant
NDA	NIMH Data Archive
NHGRI	National Human Genome Research Institute
NH&MRC	National Health & Medical Research Council
NIH	National Institute of Health
NIMH	National Institute of Mental Health
NRGR	NIMH Repository and Genomics Resource
OCTU	Orygen Clinical Trials Unit
OASIS	Overall Anxiety Severity and Impairment Scale
PGI-I	Patient Global Impression of Improvement
PI	Principal Investigator

Abbreviation	Term in Full
PICF	Participant Information & Consent Form
PNS	Persistent Negative Symptoms
PSYCHS	Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS
PUFA	Polyunsaturated Fatty Acids
RGO	Research Governance Office
RSWG	Remission in Schizophrenia Working Group
PDQ-6	Perceived Deficits Questionnaire
PRS	Polygenic Risk Score
RA	Research Assistant
RDoC	Research Domain Criteria
RFA	Research Funding Announcement
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SIPS	Structured Interview for Psychosis Risk Syndromes
SIS	Suicidal Ideation Screen
SMART	Sequential Multiple Assignment Randomized Trial
SNP	Single-Nucleotide Polymorphism
SOFAS	Social and Occupational Functioning Scale
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UHR	Ultra High Risk for psychosis*
WASI-II	Wechsler Abbreviated Scale of Intelligence
YRC	Youth Research Council

*Note: Clinical High Risk (CHR) is the terminology used in the US. Ultra High Risk (UHR) is used in Australia. For the purpose of protocol harmonisation with the US-based research network (ProNET), the term 'CHR' is used in this document. However, the term 'UHR' will be used in participant facing materials in order to maintain consistency with clinical service language.

4. Study Synopsis

Item	Description
Study Type	Non-interventional
Study Population	The study cohort will consist of young people aged 12 to 30 years (inclusive) who are (1) at clinical-high risk of psychosis (CHR) or (2) healthy control participants (HC).
Sample Size	The overall sample size is N=1,187. This includes 937 CHR and 250 HC participants. The participants will be recruited across a network of Australian and international clinics.
Total No. of Study Centres	11 study centres: nine international sites and two Australian hubs. Additional recruitment sites may be added or removed as required.
Study Design	Non-interventional study examining clinical trajectories and predictors of outcome in the CHR clinical population. The CHR cohort will be followed longitudinally for 24 months and will receive treatment as usual. The HC cohort will be assessed at baseline. A subset of the HC cohort will receive repeat assessments at 2-month follow up. HC's will also be contacted by Research Assistants at Months 12 and 24 to determine possible onset of CHR status or a psychiatric diagnosis.

Study Context & Rationale	Detection and intervention before psychosis develops, when individuals are at clinical high risk for psychosis (CHR), could attenuate, postpone, or even prevent the conversion to psychosis and improve individuals' clinical and functional outcomes. The Accelerating Medicines Partnership in Schizophrenia (AMP SCZ) is a US-based public-private program with the overall aim of generating tools that will *considerably improve success in developing early stage interventions for patients who are at risk of developing schizophrenia and other psychotic disorders*. The current AMP SCZ 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). 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 (e.g., non-remission of CHR status, functioning, anxiety, depression, and substance use disorders), and define targets for treatment development. Such tools will enable clinical trials to test new pharmacological interventions that may prevent or delay the onset of psychosis. In order to realise the aims of AMP SCZ, NIMH released a Research Funding Announcement (RFA) in December 2019 to fund CHR Research Networks to collect multimodal data in large samples of CHR patients. Two international networks were funded: PRESCIENT, led by researchers based at Orygen (PI Nelson), and ProNET, led by US-based researchers (PI Woods). The current Human Research and Ethics Committee submission relates to the PRESCIENT Research Network. Additionally, a Data Processing, Analysis, and Coordinating Center (DPACC; PI Shenton, Harvard University) was funded, with the purpose of integrating and analysing data from new and key existing clinical high risk cohorts, including the AMP SCZ cohort. Findings from AMP SCZ will enable researchers to develop algorithms that predict the course of illness for clinical high risk individuals, allowing for early intervention and testing of treatments that may prevent the development of schizophrenia and other psychotic disorders and reduce their impact. All AMP SCZ data and analyses will be made publicly available through the NIMH Data Archive. Through rapid data sharing and integrated, collaborative research, AMP SCZ will enable proof-of-principle clinical trials to test tools and hypotheses that emerge from the initiative.

Primary Objectives	**1. CHR Network Consolidation:** Use the Australian Early Psychosis Collaborative Consortium (AEPCC) national platform to consolidate a network of CHR recruitment centres organised according to a 'hub and spoke' model, with Orygen functioning as the central hub with 1 Australian and 9 non-Australian clinics as spokes. The network will: recruit a large sample of CHR patients (n=937) and a healthy control (n=250) sample; implement repeated multimodal assessments; map trajectories and outcomes over a 2 year period (conversion to psychotic disorder, persistent and incident non-psychotic disorders, non-remission of CHR status, persistent negative symptoms, psychosocial functioning, full recovery). This network of CHR recruitment centres will provide the clinical research infrastructure for future treatment trials in this clinical population informed by findings from the current program of work. **2. Prediction:** In collaboration with the NIMH Steering Committee and the DPACC, the PRESCIENT dataset will be used to: 2a. Test the external validity of existing and forthcoming prediction models in the field (e.g., NAPLS, EU-GEI, PRONIA, PSYSCAN). 2b. Implement the model with strongest performance as an online risk calculator that can be calibrated for service setting (primary vs specialist settings) and availability of type of data (e.g. clinical data alone, clinical data plus neurophysiological data, polygenic risk score, etc). 2c. Use the full AMP SCZ dataset (combined PRESCIENT and ProNET data) to develop new, more refined prediction models and risk calculators using recent theoretical and methodological advances (e.g., dynamic prediction, probabilistic multimodal modelling) and a range of biomarkers. These tools will be of clinical utility in decision making about stepping interventions up/down as risk is assessed over time (clinical trajectory, treatment response) and in response to incoming biomarker information, as well as guide stratification of patients in future clinical trials. **3. Validation:** Internally and externally validate the prediction models generated using the AMP SCZ dataset. This will test the robustness, replicability and generalisability of the models' performance. The national and international network of sites and research specialisation will provide the clinical research infrastructure for future treatment trials in this clinical population informed by findings of the current program of work.
Study Endpoints	Clinical data will be collected up to the 24-month follow-up time point. See the assessment schedule (section 8.1) for each component end-point.

Inclusion Criteria	**ALL** 1. Aged 12-30 years inclusive 2. Understand and sign informed consent/assent 3. Meet either CHR or HC criteria **CHR** Meet diagnostic criteria for CHR (Vulnerability Group; Attenuated Psychotic Symptoms Group; Brief Limited Intermittent Psychotic Symptoms Group) as determined using the PSYCHS. **HC** Healthy control participants will be recruited from the community. HC must not meet any of the exclusion criteria and must not: 1. Meet CHR criteria or have a current or past Cluster A personality disorder. 2. Be receiving any current treatment with psychotropic medication. 3. Have a family history (in first-degree relatives) of psychotic spectrum disorders.
Exclusion Criteria	1. Antipsychotic medication exposure equivalent to a total lifetime haloperidol dose of >50 mg, estimated based on available information (e.g., medical file documentation, patient, and family report). 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 psychotic disorder, verified using the SCID.
Data Sources	Demographic, clinical, neurocognitive, neurophysiological, neuroimaging, digital, speech and biospecimen data will be collected.
Control Group	Healthy controls
Study Duration	November 2021-December 2025
First Patient First Visit	November 2021
First Patient Last Visit	November 2023
Last Patient Last Visit	November 2025
Data Analysis	A range of statistical analyses and machine learning approaches will be deployed to test study aims. The NIMH-funded US-based Data Processing and Analysis Coordination Centre (DPACC) will lead data analysis, with input from PRESCIENT and ProNET investigators.
Funding Provided by	National Institute of Mental Health (NIMH)

5. Introduction

5.1. The Accelerating Medicines Partnership (AMP)

The Accelerating Medicines Partnership (AMP) is a public-private partnership between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), European Medicines Agency, and multiple public and private organizations. Managed through the Foundation for the NIH (FNIH), AMP aims to identify and validate the most promising biological targets for therapeutics. The ultimate goal is to facilitate successful development of pharmacological treatments for this early stage of psychotic illness.

There have been a number of AMP projects focused on disorders such as Alzheimer's Disease, Parkinson's Disease, and diabetes1. AMP Schizophrenia (AMP SCZ) marks the first AMP initiative focused on a neuropsychiatric disorder and the fifth AMP initiative overall. The overall aim of AMP Schizophrenia (SCZ) is to generate tools that will considerably improve success in developing early stage interventions for patients who are at risk of developing schizophrenia and other psychotic disorders (see full details here: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/schizophrenia). The AMP SCZ current partners include government partners (NIH, FDA, European Medicines Agency), industry partners (Boehringer Ingelheim, Janssen, Otsuka), non-profit partners (American Psychiatric Association Foundation, National Alliance on Mental Illness, One Mind, Schizophrenia and Psychosis Action Alliance, Wellcome). The approach is pre-competitive, i.e., research conducted cooperatively without potential marketing activities or patenting, with the goal of accelerating and advancing research outcomes. The funding for AMP SCZ totals USD 99 million over a 5 year period.

5.1.1. The Need for New Therapies

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.

5.1.2. The AMP SCZ Approach

Advancing preventive interventions for schizophrenia and other psychotic disorders requires a more complete understanding of the clinical and biological predictors in the early stages of the illness. AMP SCZ will harness the power of open science to accelerate the research and development process and advance promising therapies for individuals at risk of developing these disorders. By combining the expertise and resources of public and private partners, AMP SCZ will provide the support needed to determine which biomarkers show the greatest potential for predicting progression of the disease in clinical high risk individuals.

A core component of AMP SCZ is establishing a research network focused on individuals who are at clinical high risk, identifying biological markers, clinical endpoints, and other measures that predict disease trajectory and outcomes in this clinical population.

To this end, NIMH released a Research Funding Announcement (RFA) in December 2019 to fund one or two CHR Research Networks. Two international networks were funded: PRESCIENT, led by researchers based at Orygen (PI Nelson), and ProNET, led by US-based researchers (PI Woods). The current Human Research and Ethics Committee submission relates to the PRESCIENT Research Network. Additionally, a Data Processing, Analysis, and Coordinating Center (DPACC; PI Shenton, Harvard University) was funded, with the purpose of integrating and analysing data from new and key existing clinical high risk cohorts, including the AMP SCZ cohort. Findings from these studies will enable researchers to develop algorithms that predict the course of illness for clinical high risk individuals, allowing for early intervention and testing of treatments that may prevent the development of schizophrenia and other psychotic disorders and reduce their impact. All AMP SCZ data and analyses will be made publicly available through the NIMH Data Archive. Through rapid data sharing and integrated, collaborative research, AMP SCZ will enable proof-of-principle clinical trials to test tools and hypotheses that emerge from the initiative.

5.1.3. Harmonisation of Data collected across the Research Networks

All of the assessment domains, instruments and measurement time points to be used in PRESCIENT were decided through an extensive process of team discussion involving representatives from NIMH, PRESCIENT, ProNET, the DPACC, and AMP SCZ partners. This discussion led to a consensus-based harmonised assessment battery, i.e., a common battery of assessment domains and measures that will be used across both recruitment networks (PRESCIENT and ProNET), allowing data to be pooled across both samples, increasing statistical power and generalisability of findings.

5.2.Clinical High Risk for Psychosis: Background and Significance

The 'clinical high risk' (CHR) for psychosis criteria prospectively identify young people at risk of psychotic disorders (i.e., individuals who may be in the prodromal phase of psychosis)[1, 2]. The CHR criteria have been well-validated, with approximately one third of CHR individuals converting to a psychotic disorder over a 3-year period, a rate considerably higher than in the general population and other clinical populations[1, 3, 4]. The CHR approach introduced a new paradigm to psychosis research and has been remarkably influential, with the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) including 'Attenuated Psychosis Syndrome', based on the CHR criteria, as a condition requiring further research[5].

There is *substantial heterogeneity* in clinical trajectories in the CHR population. For example, in a recent analysis of data from our multisite international trial of omega-3 fatty acids ('Neurapro'[6]) we identified 17 different trajectories in this clinical group[7] (see Fig 1 for the most common trajectories). The field is currently unable to reliably identify these trajectories early on, particularly at an individual patient level. The models to date (using clinical, neurocognitive, neuroimaging, neurobiological and genetic data) have yielded only modest predictive value for conversion to psychotic disorder and other outcomes[3, 8, 9]. This presents a challenge for targeted intervention and developing robust aetiological models. There is also now increased recognition of the CHR phenotype as a syndrome in itself, rather than merely being a risk syndrome, supported by meta-analytic evidence that CHR patients are characterised by consistent and large impairments in functioning and reduction in quality of life similar to those in other coded psychiatric disorders[10-12]. In addition, there is strong evidence that CHR status is a marker of illness severity and poor prognosis transdiagnostically[13-15]. Therefore, enhancing prediction of the full spectrum of outcomes in the CHR population (conversion to psychotic disorder, persistent and incident non-psychotic disorders, non-remission of CHR status, poor functioning etc.) is of critical importance[16, 17]. Enhanced predictive accuracy of these outcomes would be a substantial step forward in facilitating treatment development and developing aetiological models of psychosis and psychiatric disorders more broadly.

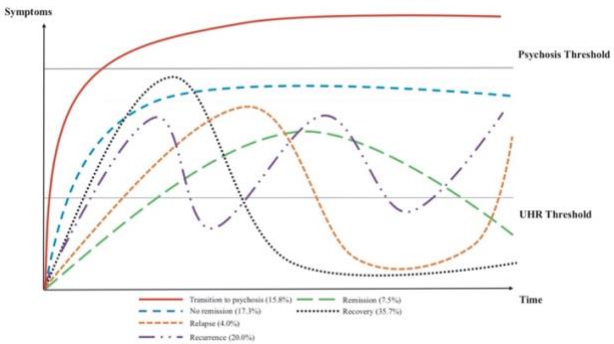

Figure 1. The most common clinical trajectories identified in a CHR sample (n=202) over a 12-month period[7].

The current study aims to recruit a large sample of CHR patients in order to develop refined prediction models for stratification of patients in clinical trials and as tools for use in clinical practice. This will lead to substantial benefits for clinical care (e.g., using dynamic risk calculators to estimate the risk for a range of outcomes for individual patients, inform personalized treatment strategy, and serve as measures of early treatment effects), healthcare services (informing decision-making regarding allocation of resources), and for research in this field (stratification of samples for treatment trials, directing the engagement of treatment targets, and refining aetiological models).

Specifically, we will:
1. Use an existing nationwide clinical infrastructure and nine international clinics (the PRESCIENT network) to support recruitment and follow up of a large cohort of CHR young people (n=937) and a healthy control group (n=250). Recruitment will occur over 2 years and participants will be followed for a 2-year period with repeat assessments over this timeframe. Biomarker assessments will be repeated 2 months after baseline in CHR participants and in a subset of healthy control participants.
2. Use this dataset to: a) validate existing and forthcoming prediction models and b) draw on the full AMP SCZ dataset to develop new, more refined prediction models using recent methodological advances and exploratory biomarkers.
3. Externally validate the prediction models generated in the AMP SCZ dataset using a subsample of the cohort. This will test the replicability of the model's performance and the generalisability of the findings to diverse healthcare settings.

5.3.The Current Project: The PRESCIENT Research Network

5.3.1 Nationwide network of early psychosis services and youth mental health services

In 2015, Orygen established the Australian Early Psychosis Research Network as a collaborative venture linked to the new development of the Federal government funded *headspace* Youth Early Psychosis Program (HEP) service platform, which we designed and advocated for[18]. The aim of this network was to bring together key researchers from a diverse range of services in Australia including the HEPs, with an interest in clinical research in early or emerging psychosis. In 2019, the Australian Early Psychosis Collaborative Consortium (AEPCC) was established, with funding support from the Wellcome Trust, introducing a national platform for a Clinical Registry (CR) and Clinical Trial and Translation Network (CTTN). The AEPCC lead investigators are represented in the current application. The foundation members of AEPCC include all HEP services across Australia and Orygen clinical services, which provides comprehensive mental health care to 15-25 years olds in Northwestern Melbourne (see Fig 2a). This reflects the uniformity of purpose and potential for momentum and uptake in the Australian early

psychosis sector. The assessment and treatment provided in these services has been subject to a stringent fidelity process directed by Orygen. The AEPCC CR and CTTN is set to realise the potential of the Australian Early Psychosis Research Network (AEPRN) and lead to activation of a proposed national Child and Youth Mental Health Clinical Trial Network (CYMHCTN).

Over the last fifteen years, the research team and other members of the Orygen clinical academic leadership have developed a youth mental health service model that has been implemented nationally through the *headspace* platform. *Headspace* is an innovative system reform and development that received policy commitment, funding and national roll-out by the Australian Federal Government, starting in 2006. It has involved the creation and upscaling of a nationwide platform of care, which has already enabled access to care for over 524,800 young Australians with emerging mental ill health[19], with evidence of clear positive impact[20]. *Headspace* is essentially a 'one stop shop', universal access stigma-free model of care for young people and families experiencing early stage mental disorders[21-25]. Orygen conceived, designed and implemented this reform which has now expanded across the country to 110 centres with 150 being active by 2022 (see Fig 2b). The *headspace* centres provide the case detection and referral platform for the co-located HEPs, resulting in a low stigma and high volume pathway into specialist early psychosis services.

The current network (PRESCIENT) will recruit across Orygen specialist programs and clinical services, one national HEP program, as well as nine international sites. Orygen clinical services consist of two tiers of care that are seamless and fully integrated: one tier consists of broad, primary care youth mental health services (5 *headspace* clinics in Northwestern Melbourne) and a secondary care tier that provides specialist early psychosis services across the same region (Orygen Specialist Program, Melbourne Health). The PRESCIENT network has partnered with international centres across Europe and Asia for the current program of work.

5.3.2 Leveraging the nationwide network for CHR recruitment (aim 1)

The clinical infrastructure described above provides clinical services for young people with a range of clinical presentations. In the 2018-2019 financial year, approximately 3,000 young people accessed HEP services, 1000 young people accessed Orygen Specialist Program, and over 5,000 young people accessed the 5 *headspace* clinics involved in the network (i.e., 6000 across the clinics directly operated by Orygen)[19]. Data on CHR status of this pool of patients is available from a range of sources including our cohort studies[26, 27], the Staged Treatment in Early Psychosis (STEP) study[28], and clinical service records. These data sources indicate that 15% of HEP patients, 15% of Orygen Specialist Program patients, and ~30% of *headspace* patients meet CHR criteria. In raw numbers, this translates to ~2,000 CHR patients/year. Therefore, our recruitment target of 468 CHR patients per year over a two-year period (937 in total) equates to recruiting <25% of the pool of eligible patients. This is highly feasible, given that recruitment rates to current CHR studies being conducted by our group (across the same clinics) consist of 50% of eligible patients.

5.3.3 Extending minimal data sets in order to test and develop prediction models

Both the *headspace* and HEP clinics provide a sampling frame with linked minimal data sets. Our network of *headspace* clinics collect a minimal data set as part of routine clinical practice[25, 29]. The AEPCC will establish a clinical registry for all early psychosis patients, including CHR patients. While these minimal data sets are invaluable for better characterizing this clinical population and standardizing assessment and routine data collection practice, they are *not sufficient for building and testing prediction models with high levels of accuracy*, which is required in this research field.

The minimal data set of *headspace* patients includes: reason for presentation, Kessler Psychological Distress Scale (K10), stage of illness, diagnosis, and functioning[25]. The HEP minimal data set includes demographics, referral pathways, prior treatment, stage of psychotic illness (CHR or FEP, determined using the Comprehensive Assessment of At Risk Mental States [CAARMS]), general distress (K10), functioning (Social and Occupational Functioning Assessment Scales [SOFAS]) and quality of life, and details of treatment received, including medication, inpatient admissions, psychosocial treatment, and patient and family satisfaction with treatment.

In the current study, we will work with the Data Processing, Analysis, and Coordination Center (DPACC) to build on these minimal data sets to collect a far more comprehensive data set, supported by a number of conceptual and analytical advances in the field, but also balanced with issues of feasibility and awareness of participant burden. We briefly summarise these conceptual and analytical advances below.

Dynamic prediction, early warning signs and network theory: Over recent years, in collaboration with European colleagues, we have approached modelling and predicting onset and evolution of psychotic disorder and other mental disorders through a dynamic (i.e., time-dependent or time-variable) lens in order to supplement the standard static prediction approach that relies exclusively on baseline (clinic or study entry) data[30-36]. This draws on approaches that have proven to be useful in other areas of psychiatry (e.g., predicting relapse in depression[37, 38]) and which have yielded greater predictive accuracy in other areas of medicine, such as cardiovascular research[39] and oncology[40], as well as in other disciplines that model complex systems, such as ecology[41, 42] and economics[43]. Consistent with our clinical staging model[44-46], this dynamic approach to prediction is well-suited for incorporating the highly changeable and mercurial nature of psychopathology, particularly in the early stages of disorder[34]. Analytical tools to operationalise these dynamic approaches include various forms of time series analysis, joint modelling, and network analysis.

Time series analysis involves analysis of a series of data points indexed in time order. Patterns in the data that emerge over time can be used for the purpose of forecasting future values. This approach has been more widely deployed in other areas of psychiatry, e.g. depression and transdiagnostic prediction[36, 38, 47, 48], than in psychosis prediction. In these other areas, particular temporal patterns in the data, including increase in emotional state correlating with itself over time ('temporal autocorrelation') and increased variance and

change in the association between emotions over time have proven valuable as 'early warning signs' of an imminent change in mental state (e.g., 'tipping point' into a depressive episode)[38, 48, 49]. In the area of psychosis and psychosis risk, the focus has instead been on the proximal relationship between everyday events/contexts and momentary fluctuations in mental state, such as stress sensitivity assessed using ecological momentary assessment (EMA), rather than on prediction of clinical outcomes[50-53].

Joint modelling is an emerging statistical methodology that uses longitudinal, repeat assessment of variables ('time-dependent predictors') to predict outcomes with variable time frames. It is therefore a useful means of *adjusting prognosis* for patients as relevant variables are assessed repeatedly over time, yielding dynamic risk calculation. Our group, led by Associate Investigator Yuen, has already introduced this approach to CHR prediction research[30-33]. In this work, a joint model using repeat monthly assessments yielded superior prediction statistics for conversion to psychosis compared to static baseline assessment in the same CHR cohort[31, 33]. Comparing the receiver operating characteristic (ROC) curves, the area under the curve (AUC) of the joint model was significantly greater than that of the baseline model (p-value=0.019). Also of note is that, for the point closest to the ideal point (0,100), the joint model showed substantially higher sensitivity (83% vs. 69%) and similar specificity as the baseline model (72% vs. 74%), indicating that the joint model was able to detect more converted cases yet with little increase in false positive rate. The strong predictive performance of this approach has recently been confirmed by another group in an independent data set[54].

Network theory posits that symptoms are not all explained by a shared underlying cause, as in the traditional latent disease model (e.g., lung cancer being the underlying common cause of various symptoms such as shortness of breath, chest pain, and coughing up blood)[55]. Rather, mental disorders are seen as complex dynamic systems in which symptoms and psychological, biological and social components have autonomous causal power to influence and trigger each other[56, 57]. If symptoms form patterns of mutual reinforcement and feedback loops, the system as a whole may become trapped or 'locked' in a state of extended symptom activation, a point at which a mental disorder may be diagnosed (e.g., conversion to psychosis). Network analysis models the pairwise relationship ('edges') between symptoms ('nodes') cross-sectionally and dynamically over time (using time series), showing interactions between symptoms[55]. It is plausible that this 'locked' state is more likely to occur in biologically vulnerable people; however, this process may be interrupted by psychosocial and biological early intervention strategies. These possibilities can be assessed in the current dataset by examining interactions between data modalities over time (e.g., digital momentary assessments and biomarkers), as well as modelling impact of treatment exposure.

Importantly, these approaches are well suited for modelling the natural course of disorder (e.g., increasing symptomatology) and the impact of time-varying exposures (e.g., adverse life events) as well as treatment. They can be applied to any type of data. Although phenotypic data has been the principal type of data used in these analytical approaches to date, they can also be applied to biomarker data. For example, persistent language disturbance[58], accelerated grey matter loss[59] or decreases over time in EEG-assessed

mismatch negativity[60] or N-1 suppression scores[61] would all be appropriate for statistical modelling using these approaches. These dynamic analytical approaches will be applied to the data collected in the current network, in collaboration with the DPACC.

Multimodal prediction: In addition to dynamic prediction approaches, multimodal (using multiple assessment domains or levels of analysis) have also proven valuable in enhancing predictive accuracy. An example of this approach is probabilistic multimodal modelling using the odds ratio form of Bayes' Rule to develop probabilistic models of outcome (e.g., conversion to psychosis) based on data from combining different modalities (e.g., clinical data alone vs clinical data plus neuroimaging data vs clinical data plus neurocognitive plus neuroimaging data)[62, 63]. Recent empirical work by the research team has indicated that this approach can improve on prediction based on data from one domain alone[63]. For example, we recently showed that a probabilistic multimodal model combining clinical history, symptoms, and fatty-acid biomarkers identified over 70% of CHR cases who converted to psychosis within one year, compared with 28% identified by standard CHR criteria[32, 63]. This approach in fact models, and can be used to further refine, real clinical decision-making regarding the need for further types of diagnostic assessments based on outcomes of each step in assessment, accounting for the baseline risk of conversion in the population from which the individual derives (e.g., help-seeking in a specialist clinic vs general population samples). This can directly inform indicated treatment based on level of risk established. Similarly, in the EU-based PRONIA study[64], supplementing clinical ratings with structural imaging (MRI) was found to increase predictive accuracy for functional outcome in CHR patients from 77% (clinical measures alone) to 83% (clinical measures + MRI). However, adding different data types has not always been found to increase predictive accuracy substantially. For example, Perkins et al[65] recently found that adding a polygenic risk score (PRS) to a risk calculator based on patient history, clinical variables and neurocognitive variables only modestly improved psychosis risk prediction. There is, therefore, a need to further identify the *types of data* that provide the greatest predictive accuracy, which types of assessments to prioritize, and in what *context* (e.g. specialized vs primary health care settings) multimodal prediction approaches are feasible and useful in predicting outcomes for individual patients. These issues will be addressed in the work of the current network.

5.3.4 Rationale for PRESCIENT assessment domains and measures

All of the assessment domains and measures to be used in PRESCIENT were decided through an extensive process of team discussion involving representatives from NIMH, PRESCIENT, ProNET, the DPACC, and AMP SCZ partners. This discussion led to a consensus harmonised assessment battery, i.e., a common battery of assessment domains and measures to be used across both recruitment networks (PRESCIENT and ProNET), allowing data to be pooled across both samples. A 2-month time point was chosen for the repeat biomarker assessments because: 1) the trajectory of change from baseline to 2 months has been found to be most useful for predictive modelling in existing data and 2) this time period can be used to inform the design of future clinical trials.

Clinical measures: Key considerations in the choice of clinical measures was to capture variables that have been found to be relevant to CHR outcomes, to capture the broad range of transdiagnostic symptomology present in this clinical population, and to minimise participant and assessor burden. As per previous studies, these measures will be integrated into a seamless clinical interview schedule.

Digital momentary assessments: Digital momentary assessments provide an ideal way of collecting data for digital phenotyping that can be used in dynamic prediction approaches. The most widely used and validated approaches for collecting these types of data are: i) intensive longitudinal EMA, the repeated (daily) sampling of a participant's experiences and behaviours in its natural environment over an extended period of time using a smartphone app and ii) passive sensing in the form of monitoring gross motor activity (wearable accelerometer) and movement patterns (phone-based GPS data). Both approaches will be used in the current study.

Neurocognition: The neurocognitive assessment domains that have been included in the current study are those that have been found to be most relevant in previous CHR prediction research. The criteria considered in designing the battery included: being relatively culturally unbiased, computerised automated scoring, automated quality control and databasing, deployable in resource limited settings, reliability and validity, being repeatable, time efficient, amenable to advanced psychometrics, sensitive to sex as a biological factor and age effects, offering targets for treatment, being open source/public domain, amenable to remote administration, and offering genomic biomarkers.

Neurophysiology: EEG-based event-related potential and event-related oscillation measures are relatively inexpensive to acquire and provide direct measurements of summated neurophysiological activity with millisecond temporal precision. The rationale for inclusion of the paradigms and measures is summarized in the table below[60, 61, 66, 67].

Measure	Abnormal in schizophrenia	Abnormal in CHR	Predicts conversion to psychosis	Predicts CHR remission	Moderate to Strong Test-Retest Reliability	Altered by NMDA blockers in pharm challenge studies	Analog in rodent models
MMN	++	+/-	++	-	+	+	+
RP	+/-	+	+	-	?	?	+
Auditory Target P3b	++	+	++	+	+	+	-
Auditory Novel P3a	+	+	-	+/-	+	+	+
Aud Alpha Desynch	+	+	+	-	?	?	?
Visual Target P3b	+	+	+	+/-	+	+	-
Visual Novel P3a	+	+	+	+/-	+	+	+
40 Hz ASSR ITC	+	+	-/+	-	+	+	+

Resting State EEG Power Spectra, 1/f	+	+/-	+/-	+/-	+	+	+

Biospecimens (blood and saliva samples): The biospecimens chosen are based on commonly reported and novel biomarkers, and those that have shown prospective associations with illness trajectories, both of psychosis[68, 69] and mood and anxiety disorders[70]. Alterations of the levels of several immune proteins and oxidative stress markers have been described in patients with psychotic and mood disorders, and such patterns may be indicative of trait or state characteristics[71-73]. Serological studies suggest that some cases of schizophrenia and bipolar disorder may be associated with exposure to microbial infections[74]. New 'omic technologies now allow cost-effective screens of lipids, metabolites, proteins. Recent findings implicate the complement and coagulation pathway in predicting psychotic experiences and psychotic disorder[75-77], and are therefore also included in the current battery. The genetic studies of the last decade have demonstrated that psychiatric disorders are highly polygenic and pleiotropic. Polygenic risk scores (PRS) can leverage the genetic information from the large genome-wide association studies (GWAS) to predict genetic risk in clinical samples. PRS are not accurate diagnostic tools, but can be considered as biomarkers that can become part of the predictive algorithm[65]. Currently, the AUC associated with schizophrenia PRS is about 0.75, and those in the top 10% of a population distribution have an increased risk approximately equivalent to the risk of having an affected first degree relative. Blood samples will be used to isolated DNA for generation of PRS.

Evidence from two CHR cohorts suggests that the stress mediator cortisol is associated with conversion to psychosis[68, 78, 79].We have recently shown that a multisystem biomarker index reflecting immune activation, stress signalling and energy metabolism is associated with increased risk for persistent poor functioning in the CHR population[80]. Given that both systemic inflammation and HPA-axis function are implicated not only in psychosis but also in mood disorders[81], it is highly likely that such processes represent transdiagnostic risk mechanisms for emerging mental disorders, a target of investigation in the current study. Therefore, we will supplement the measurement of inflammatory response and oxidative stress via a saliva sample.

Speech and facial expression samples: Language production (e.g., indices of semantic coherence and syntactic complexity) has shown promise as a marker of psychosis risk[82, 83]. A benefit of speech samples is that they are easily obtained and highly acceptable to patients. We are currently successfully collecting a large database of speech samples in CHR and first episode psychosis patients (supported through NIMH grant R01MH115332-01) and will extend this pool of data in the current assessment battery. Speech samples will be collected both in the context of an interview with a Research Assistant and in the course of daily life via a phone-based audio diary (see 8.5). In addition, disruption in facial expressivity[84] has been found to predict conversion to psychosis in CHR samples, and has therefore been incorporated into the current battery via video recordings during the open-ended speech collection interview.

Neuroimaging: Neuroimaging studies over the past twenty years have demonstrated significant associations between alterations in brain structure and connectivity and subsequent conversion to psychosis, with clear indications that these measures can improve individual prediction[85]. There is also evidence that neuroimaging can provide predictive utility for outcomes other than conversion[64]. The neuroimaging measures included in the current battery provide a comprehensive coverage of anatomy (brain volume, cortical thickness, etc.), microstructure (white matter), and both structural and functional connectivity. Measures derived from these acquisitions have been implicated in previous studies as abnormal in CHR populations and show dynamic changes between CHR and later stages of psychosis. The selection of measures and their particular parameters is optimized for the current state of the art analyses. Tier 1 is also expected to be relevant for analysis development over the next 5 years.

5.4.Study Aims

1. CHR Network Consolidation: Use the Australian Early Psychosis Collaborative Consortium (AEPCC) national platform to consolidate a network of CHR recruitment centres organised according to a 'hub and spoke' model, with Orygen functioning as the central hub with one Australian and nine non-Australian clinics as spokes. The network will: recruit a large sample of CHR patients (n=937) and a healthy control (n=250) sample; implement repeated multimodal assessments; map trajectories and outcomes over a 2 year period (conversion to psychotic disorder, persistent and incident non-psychotic disorders, non-remission of CHR status, persistent negative symptoms, psychosocial functioning, full recovery). This network of CHR recruitment centres will provide the clinical research infrastructure for future treatment trials in this clinical population informed by findings from the current program of work.

2. **Prediction:** In collaboration with the NIMH Steering Committee and the DPACC, the PRESCIENT dataset will be used to:
2a. Test the external validity of existing and forthcoming prediction models in the field (e.g., NAPLS, EU-GEI, PRONIA, PSYSCAN).
2b. Implement the model with strongest performance as an online risk calculator.
2c. Use the full AMP SCZ dataset to develop new, more refined prediction models and risk calculators drawing on recent theoretical and methodological advances (e.g., dynamic prediction, probabilistic multimodal modelling) and a range of biomarkers. These tools will guide stratification of patients in future clinical trials and may have clinical utility in decision making about stepping interventions up/down as risk is assessed over time (clinical trajectory, treatment response) and in response to incoming biomarker information, as well as guide stratification of patients in future clinical trials.

3. Validation: Internally and externally validate the prediction models generated in the AMP SCZ dataset. This will test the robustness, replicability and generalisability of the models' performance.

The purpose of recruiting a sample of healthy control participants is primarily to model site effects of biomarker measurement, particularly for neuroimaging data. However, this cohort also serves the purpose of: providing benchmark 'normal' levels on the various measures included in the schedule of assessments; modelling age effects; and assessing the stability of the biomarkers in healthy individuals.

5.5.Study Endpoints and Outcome Measures

Participants will be followed up at regular intervals over a 24-month period (see assessment schedule in 8.1). The primary outcome timepoint of interest is the 24-month follow point. Outcomes of interest are listed below:

Conversion to psychotic disorder. This is operationalised, as:

(A) At least one full threshold positive psychotic symptom as operationalised using the PSYCHS for one week or longer occurring (i) for more than an hour a day, 3-6 days per week OR (ii) daily for less than one hour

OR

(B) At least one full threshold positive psychotic symptom with the above frequency but lasting less than one week in the context of newly prescribed or newly increased antipsychotic medication

OR

(C) At least one full threshold positive psychotic symptom that is immediately dangerous – as assessed by the treating psychiatrist.

The projected number of converted cases across AMP SCZ is 300 (15% conversion rate)[7].

Remission of CHR status[7]. The definition of remission from CHR status has previously been published[87] and is currently being used in our ongoing intervention trial[28]. It is modelled on the schizophrenia course definitions presented by the Remission in Schizophrenia Working Group (RSWG)[88] and was agreed upon using a consensus process amongst CHR clinical and research experts. It requires no longer having attenuated psychotic symptoms in the CHR range, as assessed using the PSYCHS. For the Trait and State Risk Factor and Brief Limited Intermittent Psychotic Symptoms (BLIPS) groups, remission is defined as having achieved good functioning and no longer meeting criteria for schizotypal personality disorder (if present at baseline) and not having had onset of attenuated psychotic symptoms in the CHR range.

Recovery from CHR status[7]. Remission maintained for at least six months.
Relapse of CHR status[7]. Presence of CHR status after recovery (i.e., meeting PSYCHS severity, frequency and duration criteria for CHR status after recovery has been achieved).
Persistent non-psychotic disorders. A non-psychotic disorder which is present both at study entry and at outcome time point and from which full remission has not been achieved over

the interim. This will be determined using the Structured Clinical Interview for DSM-5 (SCID-5).
Incident non-psychotic disorders. A non-psychotic disorder present over the follow up period but not present at study entry. This will be determined using the SCID-5.
Persistent negative symptoms (PNS). As per our previous research[89], and consistent with the definition of Buchanan[90], PNS are defined as the presence of at least one Negative Symptoms Inventory (NSI) global subscale score ≥3 at baseline and at follow up, a combined total score of 6 or less on the Brief Psychiatric Rating Scale (BPRS) subscales of depression, guilt and suicidality (corresponding to an average of "very mild" or less on each item), and a combined total score of 16 or less on the BPRS psychotic subscales of conceptual disorganisation, hallucinations, suspiciousness and unusual thought content (corresponding to an average of "moderate" or less on each item).
Psychosocial functioning. SOFAS score at outcome time points.

5.5.1. Primary outcome
The primary outcome of interest is conversion to psychotic disorder by 24 month follow up (definition in 5.4).

5.5.2. Secondary outcomes
Secondary outcomes of interest are: remission, recovery and relapse of CHR status, psychosocial functioning, persistent and incident non-psychotic disorders, and persistent negative symptoms.

6. Study Design

6.1.Description
This is a non-interventional study examining clinical trajectories and predictors of outcomes in the CHR clinical population. The CHR cohort will be followed over a 24-month period and will receive study assessments at regular intervals. CHR participants will receive 'treatment as usual' (i.e., treatment will not be controlled). The HC cohort will be assessed at baseline. A subset of the HC cohort will receive repeat assessments at 2-month follow up.

6.2.Study Setting
The study will recruit across the following sites:

1. Melbourne - Orygen Specialist Programs, Melbourne
2. Melbourne - headspace Glenroy
3. Melbourne - headspace Werribee
4. Melbourne - headspace Sunshine
5. Melbourne - headspace Craigieburn
6. Melbourne - headspace Melton
7. Melbourne Orygen Clinical Trials Unit, Parkville

8. Adelaide – headspace Adelaide and Adelaide HEP (headspace Early Psychosis program)
9. Gwangju Early Treatment & Intervention Team (GETIT) Clinic, Gwangju, South Korea
10. Early Psychosis Intervention Programme (EPIP) Clinic, Buangkok, Singapore
11. Academic Medical Centre (AMC), Amsterdam, The Netherlands
12. Copenhagen Research Center for Mental Health (CORE), Copenhagen, Denmark
13. The University Hospital Jena, Department of Psychiatry, Jena, Germany
14. University of Cologne, represented by the University Hospital of Cologne (UHC), Cologne, Germany
15. Treatment and Early Intervention in Psychosis Program (TIPP) & Center for Psychiatric Neuroscience (CNP), Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland
16. Forward Thinking Birmingham, Birmingham, UK
17. Department of Psychiatry, University of Hong Kong

The non-Australian CHR sites have been selected on the basis of proven capacity to recruit CHR participants, previous collaborations with the coordinating centre, high-quality assessment practices, and expertise with the proposed assessment battery.

6.3.Cohort

CHR: 937 CHR patients as determined using standardised PSYCHS diagnostic criteria (see 7.4).
Healthy control (HC) participants: 250 healthy controls will be recruited from the community.

6.4.Methodology and Design

Participants from both samples will be assessed at Baseline. Refer to Section 8.0 for a full list of the measures and their explanation. The CHR sample will be followed up at regular intervals (see 8.0) for a total period of two years. A two year follow up period has been found to capture most CHR cases who convert to psychotic disorder[91]. Contact will be made with CHR participants between assessment time points (via phone calls, text messages or emails) in order to maintain engagement and address any technological troubleshooting issues with the digital momentary assessments. It is intended that if CHR participants are unable to be re-interviewed, their diagnostic status at last clinical contact will be sourced from their medical record files and state medical records (the client management interface [CMI] database for Victoria, Australia or local equivalent). HC participants will be assessed at baseline, at 2-month follow up, and at 12-month and 24-month follow up (see section 8.0).

The **screening visit** will take approximately 2 hours to complete. The **full baseline assessments** will take approximately 9–10 hours to complete (3-4 hours for clinical assessments, 1 hour for neurocognitive assessment, 2 hours for neurophysiological

assessments, 1.5 hours for neuroimaging, 20 minutes for free speech recording, and 30 minutes for blood). A saliva sample will be also be collected during one of the baseline visits. The baseline assessments may be completed over multiple sessions in order to minimise participant fatigue. There will also be a 30-min induction/information session at baseline for the digital momentary assessment component. The approximate duration of **follow up assessments** are as follows:

- **Months 1 and 3:** (90 minutes for clinical assessment)
- **Months 2:** 7.5 -8.5 (2-3 hours for clinical assessment, 45 minutes for neurocognitive assessment, 2 hours for neurophysiological assessment, 20 minutes for free speech recording, 30 minutes for blood, and 1.5 hours for neuroimaging)
- **Months 4, 5, 7, 8, 9, 10 and 11:** 20 minutes (BPRS clinical assessment only)
- **Month 6:** 2.5 hours (2 hours for clinical assessment and 30 minutes for neurocognitive assessment)
- **Month 12:** 3.5–4 hours (2.5-3 hours for clinical assessment, and 30 minutes for neurocognitive assessment)
- **Month 18:** 2 hours (clinical assessment)
- **Month 24:** 3.5 hours (2.5–3 hours for clinical assessment and 45 minutes for neurocognitive assessment)

As an acknowledgement of the time and effort involved in taking part in the study, participants will be reimbursed as outlined below:

- $60 for the baseline clinical interview
- $40 for each follow up clinical assessment time-point
- $40 for each neurocognitive assessment
- $50 for each MRI
- $50 for each EEG assessment
- $30 for each free speech interview
- $30 for each blood test
- $30 for a saliva sample time-point which includes 3x samples over 2 hours
- Up to $150 (depending on how much the participant completes) for the digital assessment component. This will be paid pro rata in monthly instalments.

In order to acknowledge the contributions of participants who complete all assessment components and time points as part of the study (excluding the digital assessment component), a 'completion payment' of $100 ($50 for healthy controls not selected for the 2-month follow up) will also be provided to the participant at the end of the study along with their month 24 follow up clinical assessment payment.

7. Participant Population

7.1.Description

CHR patients and HC patients aged between 12-30 (inclusive). For further information about study group criteria refer to Section 7.4.

7.2.Sample Size and Power

The size of the CHR sample is primarily determined by the aim of developing a prediction model for conversion to psychosis by 24 months (the primary outcome of interest). This will be achieved by combining data from the PRESCIENT and ProNET networks (i.e., the AMP SCZ dataset as whole), given that the protocols and schedule of assessments have been harmonised across the two networks. The projected CHR sample size for PRESCIENT is 937 and for ProNET 1,040 (combined n of 1,977). There is no uniform method for determining an adequate sample size for developing a prediction model[92]. In this sample size calculation, the method recently described by Riley et al[93] was used. Minimum sample size calculations required for various scenarios are provided in table 1. below. Specifically, the sample sizes were derived for the scenarios of having low, medium or high prediction performance and also for the number of parameters in the model being 10, 20, 30, 40 or 50. Conversion to psychosis is a time-to-event outcome and therefore a survival model such as Cox regression is appropriate. The table below shows the sample sizes for the survival outcome, assuming a conversion rate of 15% over 2 years (number of events=300).

Table 1. Minimum sample sizes for survival outcome.

		Number of parameters in model				
		10	20	30	40	50
Predictive performance	low	422	843	1265	1686	2108
	medium	398	796	1193	1591	1989
	high	366	732	1098	1464	1830

It is undesirable to have the number of parameters above 30 as this would result in a prediction model that is overly cumbersome in real-world settings. As indicated in the table, the minimum sample size for a model with 30 parameters is estimated to be between 1100 and 1300. However, as in all medical research, larger sample sizes lead to more robust models and it would therefore be desirable to achieve a sample size larger than this minimum recommendation. Therefore, we aim to assemble as large a sample as possible given the constraints of the length of the recruitment period and the number of recruitment sites. The sample size calculations presented in the table indicate that the overall AMP SCZ sample size of 1,977 is adequate for developing a prediction model with ~30 parameters that has high predictive performance, while still allowing a subset of the data to be 'held back' for external validation purposes (see section 14).

In addition, a simulation analysis was performed testing the performance of a linear kernel support-vector machine (SVM) to separate an event sample (converted cases) from a non-event population (non-converted cases) using 5-fold cross-validation. Results indicated

that with the proposed sample, SVM produces a favourable BAC>70% for an event rate of >0.2 and 10% moderately predictive features in a data space of up to 5000 features.

The size of the HC sample was determined primarily to control for site effects, particularly for neuroimaging data. Based on simulation analyses in the PRONIA study dataset[64], 15 HC per MRI scanner is recommended to control for site effects. 11 MRI scanners will be used across the recruitment network (Melbourne sites 1–7 will use the same scanner). Therefore, the 250 HCs to be recruited across the PRESCIENT network is sufficient. A subset of these HC participants (70 in total: 20 from Melbourne, 5 from each of the other sites) will receive 2 month follow up assessments in order to model stability of biomarkers. A larger HC sample will be recruited at the Melbourne hub (n=100) compared to other PRESCIENT sites (n=15 per site) because a larger sample of CHR participants will be recruited in Melbourne compared to other sites and, therefore, a larger HC sample is required at that site in order to accurately match HC to CHR on relevant variables (see 7.4).

7.3.Recruitment

Research Assistants (RAs) within their respective clinical service will recruit help-seeking clients who are being cared for and supported within clinical services. The RAs will identify young people who potentially meet eligibility criteria via reviewing medical records of new referrals, consulting with clinicians working in the recruiting clinics and/or sitting in on clinical review at the respective recruitment sites or other site-appropriate study recruitment activities. This method closely aligns with other studies recruiting this clinical population. Initial suitability will be established by the fact that the young person appears to meet CHR criteria, falls within the targeted age range, appears competent to consent to the study, and there is no obvious indication that he/she meets exclusion criteria. Healthy control participants will be recruited from the community using a variety of methods, including social media posts and word of mouth as well as from an existing list of HC participants in previous studies who have indicated they would like to participate in future research projects.

7.4.Inclusion Criteria

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

Inclusion criteria for all participants (CHR and HC):

A participant will be considered eligible for inclusion in this study only if all of the following criteria apply:

(1) Aged 12-30 years inclusive
(2) Understand and sign informed consent/assent
(3) Meet either CHR or HC criteria (see below for more details)

Specific inclusion criteria for CHR participants:

The participant must be help-accepting and meet diagnostic criteria for CHR (Vulnerability Group; Attenuated Psychotic Symptoms Group; Brief Limited Intermittent Psychotic Symptoms Group), as defined using the PSYCHS.

Specific inclusion criteria for HC participants:

HC will be matched with the sex, age, parental socioeconomic status and parental education level of CHR participants enrolled at each site. HC participants must not meet any of the exclusion criteria and must not:
1. Meet CHR criteria or have a current or past Cluster A personality disorder
2. Be receiving any current treatment with psychotropic medication
3. Have a family history (in first-degree relatives) of psychotic spectrum disorders, operationalised using the FIGS.

7.5.Exclusion Criteria

1. Antipsychotic medication exposure equivalent to a total lifetime haloperidol dose of >50 mg (see Appendix A for haloperidol equivalents), estimated based on available information (e.g., medical file documentation, patient 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 enrolment.
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 (TBI) screening instrument.
5. Current or past treated or untreated psychotic episode, as determined using the PSYCHS.

7.6.Discontinuation and Withdrawal

7.6.1. Participant Discontinuation Criteria

A participant will be discontinued when the PI, Sponsor or HREC have decided that the participant will not complete the study. The status 'discontinued' is required to be documented. Discontinuation could include:
(1) Participation interferes with the appropriate clinical management of risk to self or others.

(2) An adverse event or serious adverse event leads to a request for discontinuation by an investigator or research member. These cases may be offered treatment as inpatients or via intensive community care, as per early psychosis guidelines. Data collected after meeting the discontinuation criterion will not be included in the primary analysis.

7.7.Study Discontinuation Criteria (Stopping Rules)

The study may be terminated at any time by the Sponsor.

7.8.Replacement of Participants

Participants who are withdrawn or discontinued from the study will not be replaced.

7.9. Incorrectly enrolled Participants

Incorrectly enrolled participants will be discussed by the Investigator and Orygen on a case-by-case basis, and a written decision will be made as to whether they should remain on study or be withdrawn.

7.10. Withdrawal

All participants have the right to revoke consent from the study at any time and this will be clearly stated (verbally and in writing) at the time of consent. Withdrawal from the study can be at the request of the participant. Withdrawn participants will be informed that they will no longer continue with the study protocol and that their withdrawal from the study will not influence their treatment at clinical services. Participants who withdraw from the study will always be asked about the reason(s) for their withdrawal and about the presence of AEs. Adverse events that are possibly related to study procedures should be followed up until resolution, the adverse event stabilises or the participant is lost to follow up. The participant is not required to provide a reason of withdrawal. For a participant who withdraws their consent, their data collected up to the point of withdrawal will still be used for the purposes of the research unless explicitly stated by the participant that they wish their data removed from any applicable databases.

Withdrawal can include passive withdrawal of consent (participant not lost to follow up, but not attending scheduled appointments).

Every effort will be made to contact the participant, including use of all available contact details, and consulting with the relevant clinical teams. If the participant cannot be recontacted directly, it is intended that CMI (or the relevant local system) will be used to determine if the person has had contact with other mental health services. The study team will also ask the participant to nominate at least one friend or relative who can be contacted in the event that the participant cannot be contacted.

8. Visits and Assessments

The Schedule of Assessments is shown in Section 8.1. An explanation of each measure can be found in the sections that follow. The aims of the research study will be best achieved if participants take part in *all* assessment components, as we are interested in building multimodal prediction models. Hence, participants must agree to participate in all assessments for which they are eligible. However, if a participant is ineligible to participate in a biomarker assessment (e.g., if they have braces and hence cannot undergo the MRI scan), they will still be able to participate in the study. The digital momentary assessments are an optional component of the study - participants can opt out of this component without compromising their participation in the overall study. The study visits may be split into multiple visits if this is preferred by the participant or the participant and their parent/legal guardian.

8.1.Table 2 Schedule of Assessments

✓ = CHR participants
C = HC participants (70 HCs – 20 from Melbourne, 5 from each of the other sites/hubs, will receive the repeat assessments at month 2 follow up)

		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Conversion
Informed consent																		
Domain	**Instrument/ Specimen**	**Screening**	**M0**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M18**	**M24**	
CLINICAL																		
Inclusion/Exclusion criteria	PSYCHS/SOFAS/SCID5-PD-Schizotypal /FIGS (abbreviated version)/ TBI/medication use (PharmaTreat)	✓C													C*		C*	
Medical & psychiatric history	Health and Medical Conditions Questionnaires	✓C	✓	✓	✓C	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓C	✓	✓C	
Demographics	**Demographics**		✓C															
Premorbid functioning	PAS			✓														
Adverse events	**Adverse Events**		✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	✓C	
Attenuated psychotic symptoms, associated distress, and conversion to psychosis	PSYCHS		✓C	✓	✓C	✓			✓						✓ C*	✓	✓ C*	✓C
General psychopathology	BPRS[94]		✓C	✓	✓C	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Depression	CDSS		✓C	✓	✓C	✓			✓						✓	✓	✓	
Anxiety	OASIS[95]		✓C	✓	✓C	✓			✓						✓	✓	✓	
Suicidality	CSSRS		✓C		✓C				✓						✓	✓	✓	

		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Conversion
Sleep disturbance	PROMIS-SD		✓C		✓C				✓						✓	✓	✓	
Substance use	ASSIST[96]		✓C		✓✓				✓						✓	✓	✓	
DSM diagnoses	SCID-5-RVs[97]		✓C												✓C*	✓	✓C*	✓C
Patient global impression of severity	PGI-S		✓C	✓	✓C	✓			✓						✓	✓	✓	
Psychosocial functioning	SOFAS[98], GF Social, GF Role		✓C	✓	✓C	✓			✓						✓ C*	✓	✓ C*	✓C
Perceived Stress Scale	PSS		✓C	✓	✓C	✓			✓						✓	✓	✓	
Perceived Discrimination Questionnaire	PDQ		✓C															
Pubertal development Scale	PDS		✓C															
Psychosis Polyrisk Score	PPS[99]		✓C															
DIGITAL MOMENTARY ASSESSMENTS																		
Daily changes in mental state and context	EMA		✓C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C			
Physical activity, sleep-wake cycles, travel patterns	Passive sensing (actigraphy, geolocation)		✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C			
NEUROCOGNITION																		
Premorbid IQ	WRAT 5 Reading Accuracy		✓C															
		V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Conversion**
Current IQ	WASI-II - 2-subtest version (Vocab & MR)[100]		✓C														✓	
Processing speed	Digit-Symbol Substitution Test		✓C		✓C				✓						✓		✓	

		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Conversion
Attention	Continuous Performance Test		✓C		✓C				✓						✓		✓	
Working memory	Letter N-Back		✓C		✓C				✓						✓		✓	
Relational Memory	Digit-Symbol Substitution Test		✓C		✓C				✓						✓		✓	
Spatial memory	Visual Object Learning Test		✓C		✓C				✓						✓		✓	
Verbal learning	List Learning Test		✓C		✓C				✓						✓		✓	
Emotion recognition	Emotion Recognition Test		✓C		✓C				✓						✓		✓	
Motor	Finger Tapping Test		✓C		✓C				✓						✓		✓	
Sensorimotor speed	Motor Praxis*		✓C		✓C				✓						✓		✓	
NEUROPHYSIOLOGY (EEG)																		
Mismatch negativity/visual oddball	Mismatch negativity and visual oddball		✓C		✓C													
Auditory oddball	Auditory target/novelty P300 Auditory target/novel alpha desynchronisation		✓C		✓C													
40 HZ auditory steady state response	40Hz inter-trial phase coherence, baseline inter-stimulus interval gamma power		✓C		✓C													
Resting state (eyes open/closed)	Power spectra 1/f slope		✓C		✓C													
BIOSPECIMENS																		
Vital signs	Elevated body mass index, blood pressure, temperature		✓C		✓C													

		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Conversion
Current health status and activity	Current illnesses and recent activity		✓C		✓C													
Elevations in white blood cells	Blood sample – CBC with differential		✓C		✓C													
Immune system, coagulation system, complement system, and oxidative stress	Blood sample – plasma, serum (multiplex, ELISA/mass spectrometry)		✓C		✓C													
DNA isolated for microarray/low-pass sequencing	Blood sample – buffy coat		✓C		✓C													
Functional assays for redox dysregulation and cell membranes for lipids (e.g. DHA/EPA/AA)	Whole blood sample (functional assays, mass spectrometry, gas chromatography)		✓C		✓C													
Cortisol	Saliva Collection (ELISA)		✓C		✓C													
SPEECH and FACIAL EXPRESSION																		
Language content and structure **Speech acoustics**	Free speech recording (Zoom audio)		✓C		✓C													
	PSYCHS interview recording		✓C	✓C	✓C	✓C			✓C						✓C	✓C	✓C	✓C
	Audio diaries recorded via smartphone as component of EMA (2 mins daily)		✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C	✓ C			
Facial expression	Free speech recording (Zoom video)		✓C		✓C													
NEUROIMAGING (MRI)																		
Structural/functional (incl resting state)	T1, T2, diffusion MRI, resting state functional MRI (BOLD)		✓C		✓C													

		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Conversion
TREATMENT AND HEALTH SERVICE UTILISATION	Psychosocial/ pharmacological treatment/service use		✓C	✓	✓C	✓			✓						✓C	✓	✓C	

Notes:
1. The Baseline visit needs to be conducted within 3 weeks of the screening visit. If not, the screening visit will need to be repeated. The study team will endeavour to schedule all other visits up to month 12 within +/- 1 week of their due date. For example, a Month 6 visit can occur up to 1 week prior to or after its due date. Month 18 and 24 will have a visit window of +/- 2 weeks. Assessments conducted outside these windows will be discussed with the local study team and the decision whether or not to utilize the data in analyses will be documented accordingly.
2. Converted cases will be followed up as per the schedule of assessments. This will also be the case for participants who commence antipsychotic medication after study enrolment.
3. Neurocognition tasks: Reading task in English speaking sites will be the WRAT5 Reading subtest; in non-English speaking countries the local version of the NART will be used. Apart from Premorbid and Current IQ, all other cognitive domains will be measured using the Web version of the Penn Computerised Neurocognitive Battery (PennCNB).
4. The TBI will only be completed for participants where clinically indicated (i.e., participants who have had a traumatic brain injury, as reported by the participant or family or as determined from the participant's medical history).
5. If conversion to psychosis is suspected based on the monthly BPRS assessment, then the PSYCHS and SCID will be conducted to check conversion status.
6. Study participants will be contacted in between the formal assessments for the purposes of engagement and safety follow-up (see 8.12).
** HC's will be contacted by Research Assistants at Months 12 and 24 and asked about their mood, behaviour, emotions, and other experiences since their last assessment (to determine possible onset of CHR status or psychiatric diagnosis). They will also be asked about any contact they may have had with mental health services since last visit. These check-ins will be completed using the PSYCHS, SOFAS, SPD, and the SCID 5 screening questions. If the SCID 5 screening questions indicate presence of a DSM 5 diagnosis, the relevant section of the SCID 5 will be completed. A full conversion to psychosis assessment will be administered if the PSYCHS indicates onset of psychotic disorder. These assessments will be conducted remotely (via phone or video call) and will take around 20-30 minutes. The Research Assistant can also provide a face-to-face visit if this is the preferred option.*

8.2.Demographics, Medical and Psychiatric History

Demographic information (age, sex, gender, race, ethnicity, socioeconomic status, employment, educational attainment and age and education of biological parents) and medical and psychiatric history will be collected. Prior treatment (pharmacological and psychosocial treatment and health service utilisation) will also be captured, based on information collected from the participant and, as required, medical files, family and/or pharmacist.

8.3.Clinical Assessments

Informed by the recent advances in the field (see section 5.2), the study aims to collect multimodal data (clinical, biological, genetic, neurocognitive, neurophysiological, neuroimaging), baseline and repeat assessments over time ('macro' level monthly assessments) and 'micro-level' momentary (day-to-day) data collected through digital platforms (EMA and passive sensing). The 'macro' level repeat assessments are critical for both dynamic prediction of outcomes and also accurate characterization of clinical trajectories over time.

The battery of assessments are listed in 8.1 and described below. The selection of measures is informed by the Neurobiology in Youth Mental Health Partnership[101], a national effort led by Orygen to standardize research assessments in order to create large datasets, guided by principles of feasibility, participant and clinical service burden, transdiagnostic relevance and translatability into clinical practice.

The following measures will be administered by RAs as part of an integrated clinical interview:

The **Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS)** is a semi-structured interview which assesses symptoms associated with the prodromal phase of psychosis, and which is used to define the CHR criteria and onset of first-episode psychosis (FEP). The attenuated psychotic symptoms (positive symptoms) section of the PSYCHS will be assessed at all major assessment timepoints. This will be a rating of the worst period of each symptom either (1) over the last year (at Screener) or (2) since the participant's last research assessment.

The **Structured Clinical Interview for DSM-5 (SCID-5)** is a semi structured interview guide for determining DSM-5 diagnoses. The SCID-5-Research Version (RV)[97] will be used to assess DSM diagnostic criteria for Mood and Substance Use disorders and the SCID-5 Personality Disorders (PD)[102] will be used to assess Schizotypal Personality disorder. If the participant converts to psychotic disorder, as determined using the PSYCHS, then the Psychotic Disorder section of the SCID-5-RV will be administered to determine type of DSM psychotic disorder. The language and diagnostic coverage

make the SCID-5 most appropriate for use with adults (age 18 and over); with slight modification to the wording of questions it may be used with adolescents.

Family Interview for Genetic Studies (FIGS)[103]: The FIGS, developed by NIMH, is an instrument that gathers diagnostic information on families in genetic and family studies on mental disorders, such as schizophrenia and bipolar disorders. It offers diagnostic information on each family member of the study participant. The FIGS has been found to be valid and reliable and has been used extensively in previous research. An abbreviated version will be used in the current study, limiting assessment of family history of mental disorder to psychotic, mood and substance use disorders.

The **Social and Occupational Functioning Assessment Scale (SOFAS)[98]** is a numeric scale (1 through 100) used to rate social and occupational functioning. The SOFAS focuses exclusively on the individual's level of social and occupational functioning, not symptom severity.

The **Global Functioning: Social and Role scales (GF:S and GF:R)[104]** will also be used to rate social and role functioning.

Premorbid Adjustment Scale (PAS): The PAS will be used to assess premorbid functioning across developmental periods and across a number of 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.

The **Brief Psychiatric Rating Scale (BPRS)[94]** is a rating scale in which 24 items relating to different types of psychopathology are rated on a continuum of not present to extremely severe. This measure will provide an overall measure of general psychopathology.

The **Negative Symptom Inventory-Psychosis Risk (NSI-PR)[105].** The NSI-PR was designed specifically for measuring negative psychotic symptoms in the CHR population, taking into account aspects of behaviour and socialization that are common to this age range.

The **Overall Anxiety Severity and Impairment Scale (OASIS)[95]** is a valid and reliable measure of anxiety severity and related impairment. It is a brief (five-item) continuous measure, which can be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. The total OASIS score is calculated by adding together the scores for the five questions. A score of 8 or above suggests clinically significant anxiety.

The **Patient Reported Outcomes Measurement Information System-Sleep Disturbance** (**PROMIS-SD)**[106] is a brief (8 item) measure of 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.

The Calgary Depression Scale for Schizophrenia (CDSS) is a nine item structured interview scale designed specifically to assess depression independently of symptoms of psychosis in schizophrenia[107]. It has been validated in CHR samples[108].

The **Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)**[96]**,** will be used to measure substance use. This measure is widely used and endorsed for the assessment of drug and alcohol use by the World Health Organisation.

The **Columbia Suicide Severity Rating Scale (CSSRS)**[109] assesses suicide risk through a series of simple, plain-language questions. The answers identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs. The evidence-supported C-SSRS is recommended by the Food and Drug Administration and often referred to as the gold standard for suicide risk assessment. The C-SSRS has been validated in adolescent and adults.

8.4.Self-Report Measures

The following measures will be rated by participants themselves on a tablet:

The **Patient Global Impression of Severity (PGI-S)** is a single item self-report measure assessing a patient's impression of severity of their symptoms over the last 7 days.

Perceived Stress Scale (PSS)[111]**:** The PSS is the most widely used psychological instrument for measuring the perception of stress**.** It 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.

Perceived Discrimination Scale (PDS): Perceived discrimination will be assessed using an adapted self-report measure from Jannsen et al (2003)[112]. Participants answer 'yes' or 'no' to whether they had experienced discrimination in their lifetime because of their skin colour; 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.

Pubertal Development Scale (PDS)[113]**:** 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.

Psychosis Polyrisk Score (PPS)[99]: This scale was developed based on meta-analyses of environmental risk factors for psychosis. It generates a single score indexing exposure to a range of environmental risk factors associated with psychosis. This single score can be included as a variable in the development of prediction models.

8.5.Digital Momentary Assessments

The digital momentary assessments are an optional component of the study. A decision not to take part in this component will not preclude involvement in the overall study.

There are three components:

1) ***Ecological Momentary Assessment (EMA)[114]*** via an existing smartphone app ('mindLAMP', available for Android and iOS). EMA will repeatedly measure symptoms and behaviour *in vivo*. The app will prompt participants to complete a short 1-2 minute survey once/day for 12 months assessing daily stress levels, affective states, anomalous experiences and behaviour. Using the same app, short 2 minute audio recordings (an audio diary) will be made on a daily basis. These consist of the participant being prompted to record speech about their recent experiences, events and context.

2) ***Passive Sensing:*** The 'mindLAMP' app is capable of automatically ('passively') logging context information by via mobile phone sensors. The geolocation (GPS) and accelerometer sensors will be used. The GPS sensor provides a location estimate for the participant's current location. The accelerometer sensor measures acceleration.

3) ***Actigraphy:*** Participants will wear Axivity AX3 (Newcastle upon Tyne, UK) watches (accelerometers assessing 24h gross motor activity) during the first year to measure rest-activity patterns and physical/sedentary behaviours.

Passive sensing and actigraphy data will be analysed using computer programs and algorithms. Variables extracted for analysis will include: roaming/movement patterns (e.g., distance travelled, maximum distance between two locations), location (e.g., 'home time', time spent outdoors), and regularity of movement (e.g., location entropy, diurnal movement index).

8.6.Neurocognitive Tasks

The neurocognitive tasks will be administered via computer, apart from the IQ tests.

The WRAT 5 Reading subtest is a short reading task used to estimate premorbid IQ. This task will only be administered at baseline.

The Wechsler Abbreviated Scale of Intelligence (WASI-II[162]) is a general intelligence, or IQ, test designed to assess specific and overall cognitive capabilities and is individually administered to children, adolescents and adults. Only the Full Scale IQ (FSIQ)-2 section will be completed. We will use the two subtest version to generate a Full Scale IQ. The WASI-II will be administered at baseline and 2 year (104 weeks) follow-up. As the WASI-II is not available in non-English speaking countries, non-English speaking sites will administer the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale–V (WAIS-V) for participants aged 16 and above and the Wechsler Intelligence Scale for Children–V (WISC-V) for participants under the age of 16.

A number of tasks from the web-based Penn Computerised Neurocognitive Battery (PennCNB) will be administered at baseline, 8 weeks, 26-weeks, 52-weeks and 104 weeks. They will include measures of attention (Continuous Performance Test), working memory (Letter N-Back), processing speed (Digit-Symbol Substitution Test), relational memory (Digit Symbol Recall), verbal learning (List Learning Test), spatial memory (Visual Object Learning Test), emotion recognition (Emotion Recognition Test), motor function (Finger Tapping Test) and sensorimotor speed (Motor Praxis).

The battery has an estimated administration time of 50 minutes at baseline, 28 minutes at weeks 8, 26 and 52, and 43 minutes at week 104.

8.7.Neurophysiological Assessments (EEG Recordings)

EEG will be acquired during 4 paradigms:

1. **Mismatch Negativity (MMN)/Visual Oddball Paradigm.** The participant performs a visual oddball target detection task while ignoring the auditory tone stimuli presented.

a. MMN Paradigm: Measures include
    i. Mismatch Negativity (MMN) amplitude - Pitch+Duration "Double Deviant tones".
    ii. Repetition Positivity (RP) amplitude - difference between late and early appearing standards within a local series of standards in MMN paradigm.

b. Visual Oddball Paradigm: Measures include
    i. Visual Target P300 (P3b) amplitude
    ii. Visual Novelty P300 (P3a) amplitude

2. **Auditory Oddball Paradigm:** Measures include

a. Auditory Target P300 (P3b) amplitude
b. Auditory Novelty P300 (P3a) amplitude

c. Auditory Target and Novel Alpha Desynchronization
3. **40 Hz Auditory Steady State Response**: Measures include
a. 40 Hz Inter-trial Phase Coherence (ITC)
b. Baseline inter-stimulus interval Gamma Power
4. **Resting state EEG (eyes open/eyes closed**): Measures include
a. Power spectra: delta, theta, alpha, beta, gamma
b. 1/f slope: Thought to reflect excitation/inhibition balance.

Frequency: EEG data will be acquired at baseline and at 2 month follow up. The protocol for baseline and follow up is identical. The purpose of the follow up assessment is to assess change trajectories predictive of CHR outcomes. Each EEG session will require between 90 minutes and 2 hours from set-up to clean-up.
Instruments: Identical 64-channel ActiChamp High Impedance EEG systems and an air-gapped acquisition computer and stimulus presentation device will be leased from a private vendor (NeuroSig) and installed at all sites.

8.8.Biospecimens

Biomarkers that can be quantified from peripheral tissue (such as plasma, blood cells or hair) are promising indicators of the pathophysiological processes that underlie mental disorders[115]. As such, peripheral biomarkers may serve multiple purposes, including indicating risk for onset or progression to a more advanced stage, delineating diagnostic entities or informing treatment choice. For this study, we selected biomarkers with an established association with risk and clinical outcomes, relevance to the pathophysiology of mental disorders (psychosis in particular), minimising participant burden, and limiting the invasiveness of specimen collection.

A blood sample (approximately 40ml or 2.5 tablespoons) will be collected to measure: elevations in white blood cells, as current illness may confound numerous biomarkers; biomarkers of immune system, coagulation system, complement system, and oxidative damage (from plasma, serum); DNA for polygenic risk score; and functional assays for redox dysregulation and cell membranes for lipids, e.g., DHA, DPA, AA (from whole blood).

The blood samples will be collected by a qualified phlebotomist at two separate study time points (baseline and month 2). One of the blood tubes (3ml EDTA) will be transferred to a local pathology service for immediate testing. These initial research analytical samples will be destroyed upon analysis according to the standard operating procedures of the respective pathology service. The remaining blood samples will be processed and stored in an -80 Celsius freezer at the Florey Institute of Neuroscience and Mental Health in Melbourne, Australia. PRESCIENT sites outside of Melbourne will store blood samples locally until transporting their bloods to the Florey Institute.

The samples will be shipped from the Florey Institute to a to-be-determined laboratory/ies for analysis. The blood samples and any paperwork accompanying them will be identified by a unique, study-specific code and hence no participant identifying information will be associated with the sample. The code will only be accessible by researchers and relevant study staff involved in the study and the code to link this will be stored securely.

Following the completion of analyses for the study, the remaining blood samples will be shipped to the NIMH Repository and Genomics Resource (NRGR). Samples will be stored in the repository indefinitely and made available to other researchers upon application for future research purposes.

At baseline and month 2, saliva samples will be collected to measure cortisol levels, indicative of stress response. At both baseline and month 2, two vials will be collected at time 1, two vials at time 2 (1 hour later), and two vials at time 3 (two hours from time 1). All saliva samples will be shipped to NRGR. NRGR will then ship 1 vial per time point (i.e., 3 baseline vials and 3 month 2 vials) for each participant to a to be determined commercial lab such as Salimetrics in the US for analysis and store the remaining samples for future research.

Additionally, data from the FIGS (family history of psychiatric disorder) may be used to inform genetic analyses; recorded history of health conditions may inform biomarker analysis; vital signs, current illness and recent physical activity will be captured as they may confound biomarker measurement.

The type of genetic analysis being conducted in this study is not expected to result in information about individual participants' future health, future treatment or risk of having children with a genetic disorder, or information that may be relevant to the health of family members who are not part of the project.

8.9.Speech and facial expression samples

For the central assessment, audio and video will be recorded using a web-based meeting platform (Zoom). This will consist of an open-ended conversation (approximately 20 minutes in length) to elicit free natural speech, following methods applied previously by our group. RAs use qualitative interviewing methods to elicit description of subjective experience. RAs will be trained to minimize interruption, and use clarifying questions to promote speech production. Open-ended questions were chosen for their ability to encourage introspection and longer speech samples, enabling the analysis of speech coherence and spontaneous content. Moreover, open-ended questions may help to reduce attrition by encouraging rapport building between the administrator and the participant. Two additional speech assessments

will be performed: audio recordings of the PSYCHS semi-structured interviews and daily audio diaries collected during ecological momentary assessment (EMA).

The audio recordings will be used to collect speech content/structure (semantics and syntax) and speech acoustics. For the open-ended interviews, video recordings will be used to collect facial expressions. Audio files from the open-ended and PSYCHS interviews will be sent to a transcription service (TranscribeMe) to obtain pseudo-anonymised transcripts that have been diarized and timestamped for further analysis. The software package OpenSmile will be used to extract information about speech acoustics from the open-ended interviews, the PSYCHS interviews, and the audio diary. The software package OpenFace will be used to extract information about facial expressions from the open-ended interview. Transcription of the audio diaries from EMA (see 8.5) will be processed by automated transcription.

8.10. Neuroimaging

The MRI protocol will collect 4 measurements:

1. T1 (7 min) – A Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) with high spatial resolution (1mm or better) that provides an excellent contrast between gray and white matter. This measure is required for anatomical segmentation of the brain.

2. T2 (6 min) – A fast spin echo acquisition with flip angle evolution (SPACE) acquired at the same spatial resolution as the T1. This measures is required to provide complementary anatomical information to the T1.

3. Diffusion MRI (11 min) – A multi-shell multi-band spin echo acquisition sensitive to water molecule displacement. This provides microstructural information (most robustly in white matter) as well as macroscopic structural brain connectivity measures. Multi-shell enables sensitivity to different displacement scales, enabling more complex biological models. Multi-band allows simultaneous acquisition of slices at different brain locations, shortening the length of the acquisition.

4. Resting-state functional MRI (21 min) – A multi-band gradient echo acquisition sensitive to blood oxygen levels (BOLD) most robustly in gray matter. This measure provides an estimate of functional connectivity within and between particular brain networks.

The protocol for baseline and follow up is identical. The follow up scan will be useful for incorporating into prediction models based on changes over time.

Instruments: All 3T magnets. Due to the variety of MRI systems across the different sites two tiers will be used:

1. **High end tier** (tier 1) – will use Siemens Prisma machines that are currently available or to be installed at most sites across PRESCIENT and ProNET. All Prisma sites will use identical protocols.
2. **Lower end tier** (tier 2) – for all other scanners across PRESCIENT and ProNET. These scanners include Siemens Skyra (3 sites), GE MR750 (4 sites), Siemens Vida

(2 sites), and Philips Achieva DDAS (1 site). The main differences between tier 1 and tier 2 will be in the diffusion scan, where tier 2 will not have the highest shell of diffusion weighting and may use lower spatial resolution. Due to the high instrument variability, the tier 2 protocol will not be identical across sites, although it will minimize differences as much as possible.

PRESCIENT will recruit up to 5 healthy volunteers per site to test the collection and data transfer procedures for the MRI. These pilot/technical scans will be conducted for each machine prior to the commencement of the participant research scans. A total of 250 demographically matched healthy controls; all sites also have considerable experience recruiting adolescent and young adult typically developing control subjects.

8.11. Treatment received

At each follow up assessment, treatment received since last assessment will be recorded. This will consist of both pharmacological and psychosocial treatment and service use. This information will be extracted from the participant interview and, as required, medical files, family and/or pharmacist. Participants who are started on an antipsychotic medication over the course of the study, regardless of whether they meet conversion to psychosis criteria, will be followed up as per the schedule of assessments.

8.12. Engagement Phone Calls and Text Messages

Study participants will be contacted in between the formal assessments for the purposes of engagement and safety follow-up. Potential safety data will be recorded, including any reported adverse events (AE) and serious adverse events (SAEs), and escalated in accordance with safety reporting procedures. These phone calls and texts will be used as a tool to increase engagement and potentially decrease participant attrition, as in other CHR studies being led by the research team. Participants can nominate which mode of contact they would prefer (e.g. phone call, text message etc.). As with all studies, participation is voluntary and all contact attempts will be ceased upon request.

8.13. Data from other sources

If CHR participants are unable to be re-interviewed for the follow up assessments, their diagnostic status at last clinical contact will be sourced from alternative sources, such as medical record files and state medical records (e.g., the CMI database for Victoria, Australia).

9. Safety Measures

9.1. Safety Measures

As this study is a non-interventional study, the primary interest of this study centres around the definition of the participant's CHR symptomatology. This will be tracked using the PSYCHS assessments which will include an assessment of symptom severity, but not assessment of causality or seriousness (or allocation to a specific diagnosis other than CHR status). Similarly, relevant medical history will be deemed as that reported during the baseline assessment. Further relevant medical history and adverse events will not be reported unless adverse events reported by the participant and/or other study team members are deemed to possibly having been caused by study activities (e.g., distress during interview, or because of interaction with study team).

The PI is responsible for ensuring that all study staff are aware of the following definitions and procedures:

9.2.Definitions

There will be no adverse events recorded in this study other than those outlined in the section above. Only the reports of those adverse events which are reported by the participant and/or study team member(s) as possibly having been caused by the study activities (e.g. distress during interview, or because of interaction with study team) will include separate individual assessment of seriousness and causality (all others: managed using the study assessments). If any of these self- or team-reported adverse events – causally or possibly causally related – meet standard seriousness criteria, they will be recorded and tracked as serious adverse events as per the Safety Management Plan.

9.2.1. Serious Adverse Event (SAE)

Hospital admissions which are related to an exacerbation in CHR symptomatology will not be reported as adverse events unless deemed to be causally related to the research activity.

9.3.AE and SAE Assessment

9.3.1. Causality

The causality of AEs (i.e., their relationship with study assessments) must be assessed by a suitably qualified Investigator at the study site. Assessing causality requires considering whether there was a reasonable possibility that the event may have been caused by study participation.

While in most cases, it is very difficult to categorically rule out a causal relationship, where terms such as "related," "possibly related" and "not related" are used they will be interpreted as follows:

"related" - the reviewer is confident of the causal relationship (e.g. temporal association, existing safety knowledge of the product, clinical judgement);

"possibly related" – the reviewer is not confident of the causal relationship but tends to deem there is a positive causal relationship;

"not related" – the reviewer has no reason to believe there is a causal relationship at the time of the assessment (or tends to deem there is not a positive causal relationship).

Causality of an event may be re-evaluated by the reviewer at any time, e.g. when further evidence becomes available to confirm or refute an assessment of causality. The reviewer may be any person on the study team who has been delegated this responsibility by the Investigator.

9.4.Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded and reported as per the per the Safety Management Plan (source documentation will include the study visit assessments, the Adverse Event Log and/or the Serious Adverse Event form).

9.5.Expedited and Prompt Reporting of SAEs

Any serious adverse event (causally related, as defined above) occurring during the course of the study must be reported to the Sponsor (Orygen) within 24 hours of the Investigator or designee becoming aware of the SAE. As much information as possible, as is available at the time of recording, is to be provided. The Investigator should always provide an assessment of causality at the time of the initial report. A follow-up report should be completed when outstanding information becomes available, when there is a significant change in the event or when the event resolves. The Investigator will maintain an SAE Log including all SAEs. SAEs will be reported to the governing Human Research Ethics Committee (HREC) and/or governance institutions in accordance with HREC and institutional requirements and Orygen's Safety Management Plan.

9.6.Handling in Cases of Unresolved AEs and SAEs at Completion or Withdrawal

Where possible, all study related AEs and all SAEs must be followed up until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve.

9.7. Procedures in Case of Medical Emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to manage medical emergencies during the study at the premises participants attend for study assessments.

9.8. Clinically Significant Results

The type of testing being conducted in this study is not designed to result in information about an individual participant or their family member's health. We will not provide participants with any individual results from analysis of the research samples. While we do not expect to identify clinically significant results in the samples, it is possible that findings of clinical significance to an individual's or their family member's health are incidentally identified.

Normal ranges for blood samples collected as part of this study are determined based on international consensus and population based studies. An allocated medically trained investigator will review the results and determine if they are clinically significant.

A radiologist will review all MRI scans and provide a report to an allocated medically trained investigator at each site, who will decide whether the scan may have clinical significance.

With regard to genetic analysis, a standard set of guidelines developed by the University of Queensland in line with The Human Genetics Society of Australasia (HGSA) position statement will be followed when determining and reporting incidental findings from genetic analyses https://www.hgsa.org.au/documents/item/11030.

Participants will be provided with the option of indicating if they would like to receive any incidental findings relating to their health or their family members' health. The information generated from their biospecimen and the genetic analyses may in some instances have recognised interventions that can benefit or reduce risk of harm to the participant or family members.

If an incidental finding is identified, the lab conducting the analysis or MRI scan will contact the research team so that the research team can link the participant's sample code with their personal details, enabling the team to contact the participant and their clinical team. The participant's clinical team or a suitably qualified study team member (medically trained) will contact the participant, and their parent/guardian if applicable, to let them know that an incidental finding of clinical significance was found and to offer them the option of learning about these results. If the participant and/or parent/guardian would like to know the details of these findings, the study team member will discuss the findings with them and advise on any clinical follow up that may be required. The study team member will arrange referrals for further clinical follow up as appropriate.

10. Study Oversight

10.1. Data Safety and Monitoring Committee

Due to the low-risk category of the study, as determined by the Sponsor, a formal Data Safety and Monitoring Committee will not be established. Safety and monitoring will be overseen by the Investigator team and Project Manager and managed in accordance with the Safety Management Plan as outlined in the Procedures Manual. Safety signals (AEs, SAEs, and suicidality data) will be regularly reviewed by study Project Manager/s and medically trained personnel. If required, and in consultation with the Sponsor, safety data will be reviewed by an independent committee to protect the safety and interests of participants included in the study.

11. Ethical Considerations

11.1. Review by an Ethics Committee

Prior to the commencement of the study, the protocol and any amendment(s), Participant Information and Consent Form, other information provided to participants (including advertising) and product information, will be submitted to the Institutional Human Research Ethics Committee (HREC). The approval letter should refer to the study by title, protocol number and version and dates of documentation reviewed and approved. A copy of the signed and dated letter of approval (on institutional letterhead) will be provided to the site and Orygen prior to study commencement.

During the course of the study, the Principal Investigator (or delegate)/Sponsor (or delegate) is required to submit to the HREC/RGO the following: amendments to the protocol and SAEs as per the committee's requirements, site-specific updates as agreed to by the Investigator and respective HREC/RGO, progress reports according to local regulations and guidelines, Final Study Report if applicable and any additional information as required (e.g., SAEs reported by other investigative sites, amendments safety information and significant administrative changes to the protocol).

Protocol amendments that may impact on participant safety or the validity of the study will be agreed upon by the PI and Sponsor and submitted to the reviewing HREC for approval prior to implementation. At conclusion of the study, the Investigator is required to inform the HREC in writing that the study has ended and no further activities regarding this protocol will be conducted at the site.

The Investigator will ensure that the study is performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The National Health and Medical Research Council (NHMRC) National Statement on Human Research will also be adhered to in Australia (as will the equivalent guidelines in other countries be adhered to be those nations' investigator sites).

11.2. Ethical Conduct of the Study

This study will be carried out in accordance with the Principles of ICH-GCP (as adopted in Australian or the applicable local regulatory authorities) which build upon the ethical principles contained in the Declaration of Helsinki and the Australian NHMRC National Statement on Ethical Conduct in Human Research, and the NHMRC Australian Code for the Conduct of Research or relevant local equivalents.

11.3. Consultations with the Youth Research Council

At the sponsor level, regular meetings with the Orygen Youth Research Council will take place throughout the study as required. This will ensure ongoing engagement of youth in the study process. Feedback from the Youth Research Council will be recorded and considered for future amendments.

11.4. Investigator Responsibilities

The protocol and the informed consent form must be reviewed and approved by a properly constituted HREC before study start. A signed and dated letter that the protocol and informed consent have been approved by the HREC must be provided to Orygen before study initiation. Prior to study start, the investigator is required to sign the protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Orygen monitors and auditors, HREC and regulatory authorities as required. If an inspection of the clinical site is requested by a regulator, the investigator must inform Orygen immediately that this request has been received.

Prior to participation in the research study, each participant (or participant and parent/legal guardian for participants under 18 years of age) will undergo a complete consenting interview with the delegated study team members and provide consent on the relevant HREC approved form. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements including those required for the consenting of participants considered under legal adult age

according to local laws. Investigators in countries other than Australia will adapt consent processes accordingly to meet local requirements (including ages of majority).

All eligible participants will have the study explained by the PI or the delegated Research Assistant or other study member. They will receive a full explanation, in lay terms of the aims of the study, the discomfort, risks and benefits in taking part as well as insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes and may not provide benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each participant will acknowledge receipt of this information by giving informed consent for participation in the study. Informed consent may also be provided electronically. The participant will be given a copy of the signed or electronically acknowledged Participant Informed Consent Form (PICF) to retain. All study documents will be fully approved by the HREC prior to being used for consenting purposes.

11.5. Participant Data Protection

The PICF will explain that study data will be safely stored in computer databases as well as in paper form. The maintenance of confidentiality will be in accordance with national data and privacy legislation. Participants in this database are identified by a unique participant identification number and their initials. The PICF will also explain that for data verification purposes, authorized representatives of Orygen, regulatory authorities, HREC/IRBs or sites may require direct access to parts of the hospital or practice records relevant to the study, including medical history.

12. Study Management

12.1. Monitoring and Auditing

Study monitoring will be performed in accordance with applicable regulations, ICH-GCP, and Orygen Standard Operating Procedures (SOPs). The level of monitoring required for the study will be based on a risk assessment of the study by Orygen.

During the course of the study, the Orygen monitor will regularly contact and may conduct remote visits to monitor study progress, confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support. The PI agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time of their staff to the monitor to discuss findings and any relevant issues. Site staff will be provided with monitor and back up contact details in the event they have queries or require assistance.

An audit is a systematic and independent examination of study-related activities and documents to determine whether the approved study-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Orygen SOPs and any applicable institutional requirement(s). Authorised representatives of Orygen, a regulatory authority, or the HREC may visit the site to perform audits or inspections. The Investigator should contact Orygen or designee immediately if they are contacted by a regulator about an inspection at their site. If an audit or inspection occurs, the PI and institution agree to allow the auditor/inspector direct access to all relevant documents and allocate their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

The Investigator will ensure that direct access to source data/documents for the purposes of monitoring, audits, HREC review and regulatory inspections is available throughout the study and during the record retention period. In addition, the Investigator will ensure that each study participant has consented, in writing, to their medical records for trial-related monitoring audits, HREC review and regulatory inspections.

12.2. Training of Staff

As per GCP, each individual involved in the conduct of a study will be qualified by education, training and experience to perform his or her respective task(s). The PI will maintain a record of all individuals involved in the study. The PI will ensure that appropriate training relevant to the study is given to staff, and that they will receive any new information of relevance to the performance of this study.

12.3. Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the PI and the Sponsor. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be approved by the HREC before implementation unless the safety of participants is at risk. Local requirements must be followed. If a protocol amendment requires a change to the PICF, approval of the revised PICF by Orygen and by the HREC is required before the revised form can be used to consent potential participants.

12.4. Protocol Compliance

The study shall be conducted as described in the approved protocol. All revisions to the protocol must be discussed with Orygen. The investigator should not implement any deviation or change to the protocol without prior review and documented approval from the HREC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant deviation must be documented in the source documentation. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining HREC approval

as soon as possible, the deviation or change will be submitted to the HREC for review and approval.

12.5. Study Termination

The planned start date for this study is the date of first patient first visit which we anticipate will be November 2021. The recruitment period will be for 2 years (November 2021- October 2022). The proposed completion date is the date of last patient last visit which we anticipate will be November 2025. The Sponsor, Orygen, reserves the right to terminate the study at any stage for any reason including funding considerations.

12.6. Data handling and record retention

Clinical data collected in the PRESCIENT research network will be entered in the secure online Orygen Research Project Management System (RPMS). The RPMS is login-protected and users can only access the section that pertains to their own recruitment site. Neurocognition data will be collected directly via the PennCNB website. MRI data, actigraphy data, speech samples, video recordings and EEG data will be stored in the University of Melbourne Mediaflux system (http://www.arcitecta.com/mediaflux/features/). Digital biomarker data will be recorded via the mindLAMP app and stored on an Orygen-based server.

All coded data will be transferred from the Orygen servers/University of Melbourne Mediaflux system to a secure server at the NIMH NDA (NDA Staging Environment). A copy of the data will remain at the Sponsor site on the Orygen servers/University of Melbourne Mediaflux system. The NIMH NDA Staging Environment will only be accessible by the Data Processing Analysis and Coordinating Center (DPACC). DPACC will conduct data monitoring and quality assurance checks on the data on this server. In some circumstances, the DPACC may also require access to some coded participant data on Orygen/University of Melbourne servers for QC and monitoring purposes, prior to it being sent to the NDA Staging Environment (e.g., to check raw neurocognitive scores in addition to the calculated scores transferred to the NDA). Following the DPACC review, the coded data will be transferred to the NIMH NDA Collaboration Space, a data repository maintained and sponsored by the National Institutes of Health (NIH). AMP SCZ investigators, AMP SCZ partners, FNIH and NIH staff will have access to the data in the NIMH NDA Collaboration Space for monitoring and data analysis purposes (subject to execution of an NDA Data Access Agreement). Every six months the NIMH NDA will make the curated data available to the general research community (NDA Curated Releases).

The raw audiovisual data will remain on the University of Melbourne Mediaflux system. Only processed audiovisual data (i.e., variables extracted from the raw data) will be transferred to the NIMH NDA. The raw passive sensing data, including

geolocation data, will be transferred to the NIMH NDA and included in the NDA Curated Releases. Investigators who access this raw passive sensing data via the NIMH NDA will require institutional ethics committee approval to do so (see 15.2). The reason for transferring raw geolocation data to the NIMH NDA is that such data holds significant promise for the development of novel environmental risk metrics. Providing this data to the general research community will aid the development of such measures for use in future studies, which may in turn contribute to the identification of risk and resilience factors in this high risk clinical population.

All study documentation will be retained indefinitely (following completion of the study) including participant files and other essential documents (study protocol, signed informed consent forms, correspondence, and other documents pertaining to the conduct of the study). Should the Investigator wish to assign the study documentation to another party or move to another location, Orygen must be notified.

In addition, the Investigator should notify Orygen prior to destruction of any study documentation, regardless of the timeframe lapsed.

The Sponsor should notify the Investigator/Institution in writing if/when study-related records are no longer required to be kept.

13. Data Management

13.1. Documentation

A screening log of all potential participants specific to the recruitment site will be maintained by the site. This will include potential participants who were considered but later deemed ineligible due to meeting one of the exclusion criteria or due to investigator discretion. The reasons for exclusion or refusal will also be recorded against their ineligibility/refusal status. This log will be stored securely and locally by the recruitment site. All participants who are considered for or enrolled in the study will receive an individual identification number. The RA Procedures Manual provides more in-depth information regarding the screening log and enrolment of participants. Documentation regarding potential participants and participants enrolled in the study will only be accessible to site study team members who need this information for conducting the study. Confidentiality will further be maintained by assigning each subject a study-specific number, and coding all data collected with that number, using the NIH Globally Unique Identifier (GUID) tool. All data collection media will use the study-specific identification number to link the data to one individual. Data on the RPMS will only be accessible to study team members from the same site as the participant.

Source data will be constituted as documents where the study data are first recorded. This will include the hard-copy questionnaires and measures, and raw data such as

EEG recordings and neurocognitive computer task responses. These data will be retained in a secure location at or by the recruitment site, accessible only to delegated study team members and relevant site staff.

Electronic Case Report Forms (eCRFs) will also be used for documentation and reporting data to Orygen. For the measures in which the results are entered directly into the eCRF, the eCRF becomes the source documentation.

Research Assistants or other appropriate delegates will be responsible for entering data into the eCRF.

Study monitoring will be performed in accordance with the monitoring plan developed by Sponsor Operations in conjunction with the study team and the DPACC. This will be augmented by the study's quality control plan.

13.2. Database management

Internet-based database applications will be used at Orygen and by international collaborators for the Case Report Form, with relevant data being entered online. The database applications will be modelled on previous studies that have adopted the eCRF data collection method. Data collected in the eCRF will be entered via a secure website. Access to the eCRF will be restricted to study personnel and the level of access will be set to maintain the privacy and confidentiality of participant information. Data is backed up on a regular basis and an audit trail of entered, amended or deleted data, as well as the staff member who made those changes, is retained. After any monitoring and data management queries are resolved and complete, the study database will be locked and the eCRF signed off by the PI for each participant. All data will be exported into the appropriate software to enable statistical analysis on secure Orygen or collaborator servers. All study team members will need to apply for access to the eCRF through the study's Project Manager or coordinating investigator. These processes will be recorded and kept with the study essential documentation.

This study has received funding from the National Institute of Health (NIH) in the USA, and as part of this funding agreement, pseudo-anonymised (coded) data will be submitted to the National Institute of Mental Health NIMH Data Archive (NDA) and the NIMH Repository and Genomics Resource (NRGR) based in the USA (see data flow description in 12.6). The NDA and NRGR are data repositories run by NIMH that allows researchers studying mental illness to collect and share pseudo-anonymised information with each other to progress scientific research.

The act of pseudo-anonymising information will ensure that all personal information about research participants is removed and replaced with a code number. This then becomes re-identifiable (coded) information and means the research team will have the link between the participant's personal identifying information and the coded data should the need to re-identify the participant arises. The principal investigator and

study team will keep the personal identifying information and matching unique code in a securely protected database. The DPACC will only access the coded data and will not access personal identifying information or the link between the coded data and personal identifying information. The only exception to this is that the DPACC will access dates when assessments were completed.

As described, this is an international study and international data transfer is going to occur. Data flow is described appropriately in the consent forms and in relevant data management procedural documentation. All data will be transferred securely, at highest industry standards, and in accordance with applicable privacy and confidentiality requirements.

13.3. Protocol Deviations and Suspected/Serious Breaches

13.3.1 Protocol Deviations

Deviations are any (minor or major) breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol. A protocol deviation is a less serious non-compliance with the approved study protocol. Examples of protocol deviations may include:

1) Missed visits
2) Missed assessments
3) Visits/assessments performed early or later than scheduled date.

13.3.2 Suspected Breaches

A suspected breach is a possible serious breach of GCP or the protocol which has been identified by a third party (other than the Sponsor, e.g., the investigator) but has yet to be formally confirmed as a serious breach by the Sponsor. An example of suspected breaches include missing consent forms.

13.3.3 Serious Breaches

A serious breach is a breach of GCP or the protocol that is likely to affect to a significant degree:

a) The safety or rights of a study participant, or
b) The reliability and robustness of the data generated in the study

Examples of potential serious breaches include:

- Participant Informed Consent:
- Confirmation that consent is not obtained
- Missed study visits or reduced contact due to error by study team that impacts on participant safety.

14. Statistical Methods

The details of the analytical approach will be determined based on ongoing consultation with the DPACC and the NIMH Steering Committee. A Data Analysis Team is currently being established with representatives from the DPACC, PRESCIENT, ProNET, NIMH, and AMP SCZ partners. However, a broad outline of the likely statistical methods is outlined below. It is expected that a variety of interim analyses may be agreed upon by relevant stakeholders.

Testing current and forthcoming prediction models (aims 2a, 2b)
The scale and range of data collected in the PRESCIENT network will allow external validation of existing and forthcoming prediction models in the field. Specifically, the CHR prediction models and risk calculators for psychosis conversion that have already been published, summarised in a number of reviews[8, 116, 117], will be tested for performance in this newly recruited large sample. There are also a number of forthcoming CHR prediction models that can be tested in the current dataset, including those from the EU-GEI[118], Pronia[64], Psyscan[119], and IPPACT[120] studies. The multimodal data to be collected in PRESCIENT will be of sufficient depth and breadth to test all of these models.

Of the existing prediction models in the field, the one that shows the strongest performance in the PRESCIENT sample may be made into an online risk calculator for preliminary use in some clinical settings (e.g., to allow clinical decision-making regarding the value of further assessments, such as referral for imaging), as in other areas of medicine[e.g.121], and to allow stratification for aetiological and treatment research. Importantly, because the PRESCIENT dataset will include participants recruited from both primary and specialist service settings (*headspace* and HEPs/Orygen), the risk calculator will be able to be calibrated for type of recruitment/service setting, which has been found to be an important factor in risk prediction in this field[122]. This use of the PRESCIENT dataset to externally validate existing and forthcoming prediction models will address one of the key limitations in the field[9], namely the lack of robust validation procedures on prediction models.

Developing new prediction models (specific aim 2c)
Critically, the PRESCIENT dataset will facilitate the development of new, more refined prediction models, and associated risk calculators, that take advances in the field into account (such as iterative and dynamic prediction, see 2.3) and which directly address the limitations identified in the field (lack of internal and external validation; low ratio of converted cases to number of predictor variables; lack of pre-selection of predictor variables; inappropriate methods of presenting model performance; not covarying for treatment received; insufficient use of clinical

comparison groups[9, 123, 124]). Data from the PRESCIENT and ProNET networks will be combined (i.e., the AMP SCZ dataset) for the development of these new prediction models. The primary purpose of these new prediction models will be to guide stratification of patients in future pharmacological clinical trials, in line with the overarching aim of AMP SCZ to develop new treatments for the CHR stage of illness.

There are a number of reasons that the AMP SCZ dataset will be able to *improve* on prediction models based on existing datasets and which may be far more useful for treatment decision-making and treatment development:
1. *Scale and multimodal data:* The size of the dataset (approximate CHR n of 2000) and the comprehensive suite of multimodal data will provide greater predictive accuracy in model development and allow the integration of multiple data types.
2. *Dynamic prediction:* There is compelling preliminary evidence that using repeat assessments over time can enhance predictive performance and provide early warning signs of deterioration or lack of treatment response. This modelling requires time series data, which is not extensively available in existing data sets, but will be collected in this new network. A variety of methods will be used to collect the required data (see 8.1 Schedule of Assessments): repeat biomarker data to examine predictive value of biomarker trajectories; in-person and online clinical, neurocognitive, and speech data; and digital assessment methods, including EMA and passive sensing (actigraphy and geolocation). The research team has developed and has access to world leading applications for both EMA and passive sensing. These dynamic aspects of predictive modelling may provide risk calculations based on trajectories in individual-level data and which can be updated over time in response to incoming information, providing recommendations for change in treatment approach (e.g., increase in risk indicating the need for intensification of treatment). They also have the potential to provide 'real time' indications of imminent deterioration in mental state.
3. Modelling impact of treatment: Most CHR patients included in research cohorts receive psychosocial and/or pharmacological treatment, even if 'standard care' rather than controlled trial treatment. There has been increased recognition in recent years that this treatment (both as pre-emptive and for presenting complaints) *influences outcomes*, i.e., prediction models may in fact be modelling treatment response rather than natural course of disorder, or possibly an interaction between the two[123, 125]. The impact of type/degree of treatment components delivered (e.g., psychosocial interventions, medications, nutritional supplements, etc.) will be captured and incorporated into predictive modelling.

Both traditional statistical and machine learning approaches will be deployed in development of prediction models. Statistical approaches will include Cox regression and joint modelling. While the selection of variables to be measured in the study are already informed by their predictive performance in previous studies, variable selection methods including LASSO and stepwise selection will be used to select

potential predictors in the final model. The candidate predictors include the range of multimodal assessments outlined in 8.1. Due to the high number of predictor variables, data reduction procedures may be used. Internal validation of the model will be conducted using bootstrap validation (a resampling technique). The performance of the prediction models will be assessed using measures such as sensitivity, specificity and concordance index (which should be at least 0.7 for good predictive performance). Machine learning approaches will include support vector machine (SVM) algorithms using model training and leave-one-site-out cross validation.

External validation (specific aim 3)
If a strong prediction model can be obtained, further evaluation of the prediction model will be conducted by using an external validation sub-sample from the AMP SCZ cohort. Data from a subset of sites across the two networks will be held back from the initial model development phase in order to externally validate the performance of the model. This will test the replicability of the model's performance and the generalisability of the findings to diverse healthcare settings. Calibration performance of the model will be assessed using calibration plot (plot of predicted outcome probabilities against observed outcome frequencies) and tests for calibration intercept and slope. Discrimination performance will be assessed using measures such as sensitivity, specificity and concordance index.

15. Publication and Use of Study Findings

15.1 Publications

The research team will follow the publication guidelines set out in Section 4 (Publication and dissemination of research findings) and Section 5 (Authorship) of the 2007 Australian Code for the Conduct of Research. An AMP SCZ publication policy has been established with the funding body, NIMH, outlining the types of research papers that will be published using this dataset and authorship designations. All research findings, whether containing negative or positive results, will be disseminated accurately. After approval by the coordinating/Principal Investigator, co-investigators and biostatisticians, results of the study will be published in peer-reviewed scientific journals and presented at scientific conferences. The final results will be published after termination of the study. Where participants have asked to see the results of the study, these results will be provided to them in due course. AMP

SCZ data and analyses will be made publicly available to suitably qualified researchers through the NIMH Data Archive.

15.2 NIMH Data Archive

The https://nda.nih.gov/ will provide cloud-based infrastructure to facilitate storage and analysis of AMP SCZ data. The data archive currently holds raw and derived data collected from a total of 500,000 research participants using a variety of measures, including clinical, imaging, electrophysiological, cognitive, genetic, and outcome data. All AMP SCZ data stored in the archive will adhere to the NIMH Data Archive (NDA) terms and conditions and the NIMH Data Sharing Policy. Specifically, participant data will be transferred in a privacy-enabled manner and will be protected by practices that include the removal of any personally identifiable information; accredited users will be given secure, role-based access to the data. The archive includes data dictionaries to describe and enable efficient searches across the diverse types of data.

The NDA will make curated AMP SCZ data available to the broader research community on a 6-monthly basis, in accordance with 'open science' principles. The NDA will also work with the DPACC to make data analysis pipelines available to the research community. The NDA requires safeguards and institutional protections and monitoring with clear guidelines for data use. Only investigators at approved institutions are permitted to submit a data use certification to the NDA. This is a legal document that an institution signs on behalf of the investigator. Investigators approved to access the data and their institutions must pledge not to attempt to identify any participant. Data use is restricted to research purposes only. Additionally, geolocation data is treated in the NDA with the additional safeguard that approved investigators and institutions must also receive local ethics committee approval from their institution to access the data and must undergo ongoing local ethics committee oversight.

The NDA, established in 2006, is sustained on an ongoing basis through NIMH funds.

15.3 Clinical Tool Development

As noted above, the prediction models developed through this program of work may lead to the development of clinical prediction tools. Although the precise nature of these clinical prediction tools are yet to be decided, an outline of the likely process is provided below.

The expectation is that, if a prediction model with strong performance can be obtained, the model will be accessible to clinicians and other interested parties either online, via a code repository, or through publications. Specifically, by inputting the values of the predictors from a particular individual into the model, the intent is for the prediction model to estimate the probability of conversion to psychosis (primary outcome of interest) for that individual. This probability can be regarded as a risk score and can aid clinicians to make decisions about appropriate level of monitoring, type, and duration of treatment. Examples of such prototype clinical tools ("risk calculators") are available at these online links: https://apps.konsta.com.pl/app/transpsych/#, http://riskcalc.org:3838/napls/[126]. Due to the repeat assessments and digital momentary assessments conducted in the current study, a clinical tool that provides dynamic prediction may also be developed. This would involve inputting data collected over time for a particular patient, with the "risk calculator" being updated with this newly inputted information. Further evaluation of this clinical tool will be conducted by using decision analysis to assess the clinical value of the tool by taking into account the decisions that clinicians and patients would need to make with regard to possible interventions[127]. This future work will further test and refine the clinical tool.

16. Funding

This study is funded by the National Institute of Mental Health (NIMH), US.

17. Outcomes and Significance

Psychotic illnesses usually first emerge in young people and result in widespread suffering, protracted disability, premature death, and a huge economic burden. Early intervention represents a vital strategy to reduce this burden. Psychotic disorders are preceded by a prodromal period of distress, impaired functioning and subthreshold symptomatology. Our original research operationally defined the Clinical High Risk state, which predicts a substantially increased risk of incipient psychosis. There is substantial heterogeneity in clinical trajectories in the CHR population. The field is currently unable to reliably identify these trajectories early on, particularly on an individual patient level. The models to date (using clinical, neurocognitive, neuroimaging, neurobiological and genetic data) have yielded only modest predictive value for conversion to psychotic disorder and other outcomes. This presents a

challenge for targeted intervention development and developing robust aetiological models.

The current large consortia-based project seeks to develop more robust prediction models for a range of outcomes in the CHR population (conversion to psychotic disorder, persistent and incident non-psychotic disorder, non-remission of CHR status, persistent negative symptoms, full recovery, functional outcome) and advance the introduction of risk prediction tools in clinical practice. These prediction models and associated clinical tools will be developed using multimodal data consisting of biomarkers (neuroimaging, neurocognition, neurophysiology, biospecimens), clinical data, and digital momentary assessments. The prediction models will facilitate selection of CHR patients for enrolment in clinical trials (patient stratification) and point towards targets for aetiological research and novel treatments. They will also serve as measures of early treatment effects and provide tools for monitoring disease progression and clinical and functional outcomes.

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Appendix A

Antipsychotic Dose Equivalents

The doses provided in the table below are currently equivalent to a haloperidol dose of 50 mg. 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 (Melleril, Aldazine)	2500
TPZ	Trifluoperazine (Stelazine)	125
ZPD	Ziprasidone (Geodon)	1500