Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) Overview

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AMP® SCZ: Language Team co-lead, DPACC Core 1 lead, ProNET Site PI

Disclosures

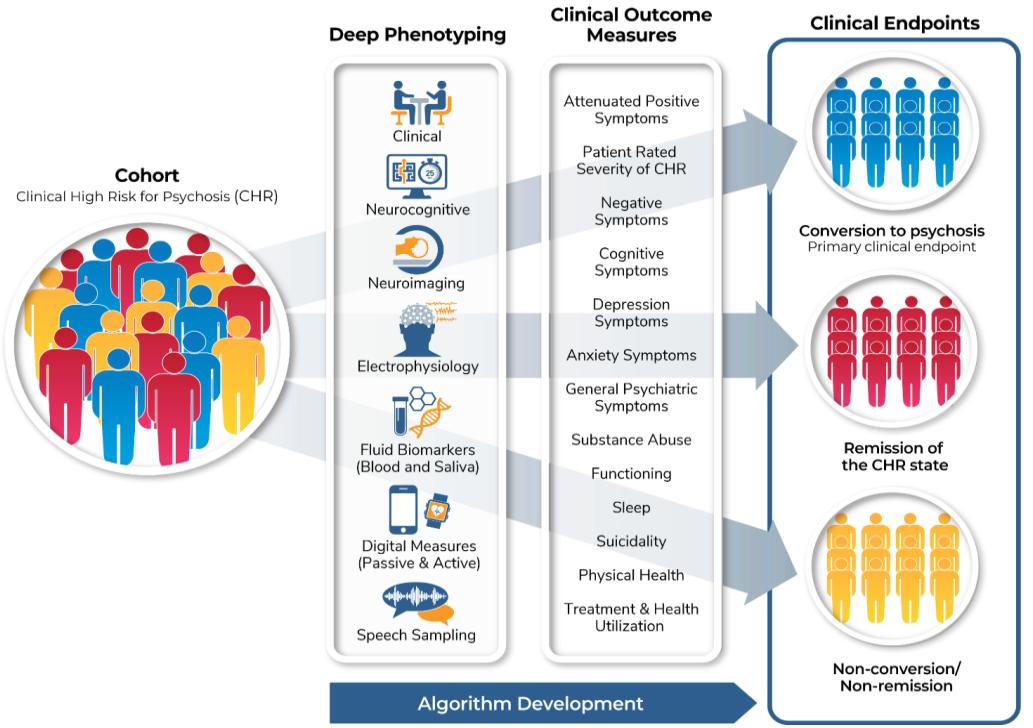
Research support from the National Institutes of Mental Health and the Broad Institute.

AMP SCZ Program Goals

AMP SCZ is a large, international collaboration focused on developing and implementing a set of tools to create multimodal algorithms that distinguish trajectories and endpoints in individuals at ***clinical high risk for psychosis (CHR)*** *–conversion, remission, and unremitted symptoms.*

Observational Study: Provide tools to enable selection of enriched patient populations and develop/validate biomarkers and outcome measures that can establish early indicators of pharmacologic treatment efficacy.

Proof of Principle (PoP) Trial: Evaluate the utility of biomarkers and outcome measures used in the observational study during a PoP trial using a pharmacological intervention(s) and determine if there is a detectable biological, cognitive, digital, or clinical signal(s) within a 12–16 week period of study.



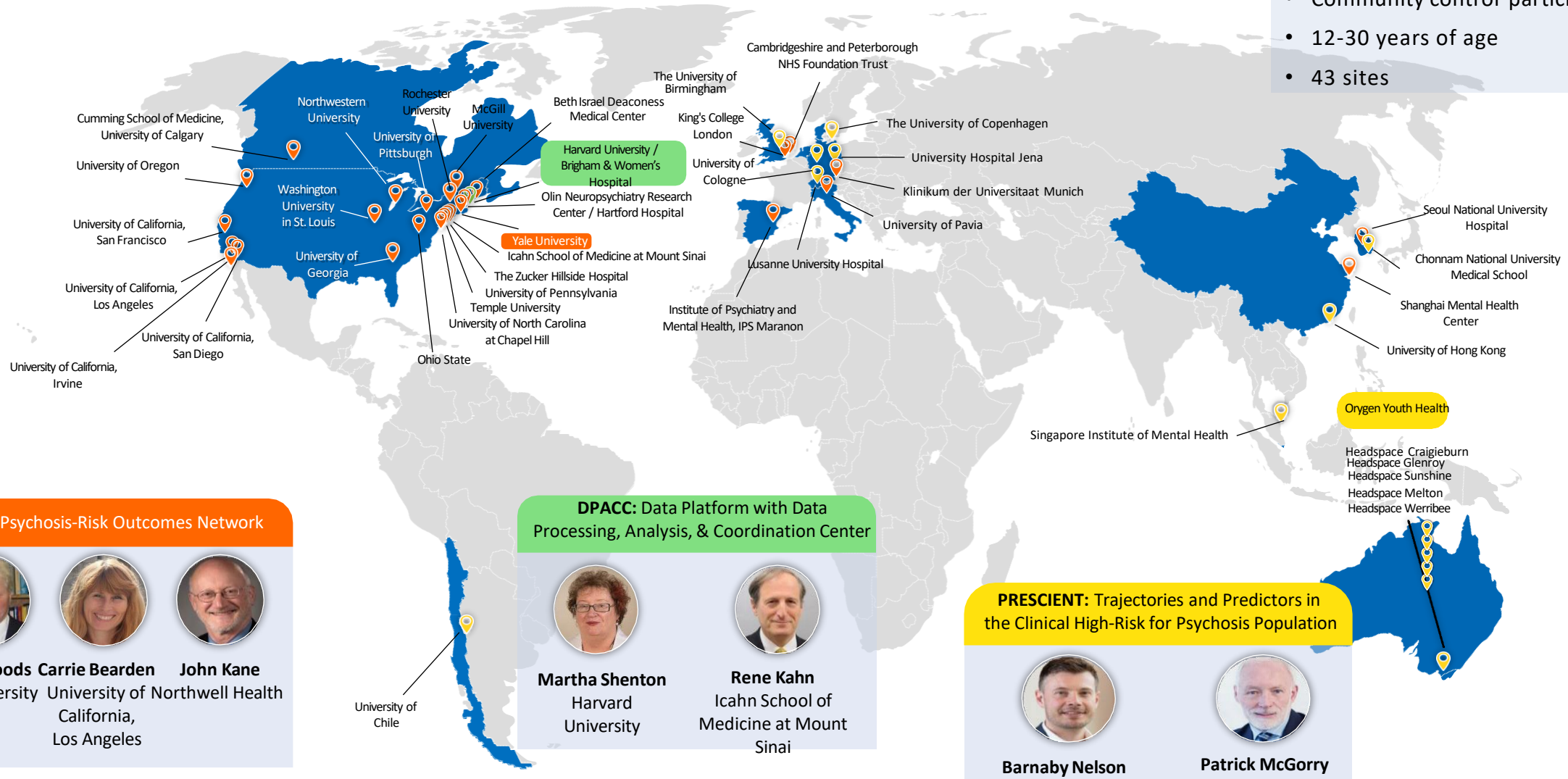
The PoP trial design will be informed by the learnings from the observational study.

AMP Schizophrenia

Harmonized Research Network & Data Processing, Analysis, and Coordination Center

Recruitment launched in Q2 2022
Enrollment completed in Q1 2025

- CHR participants:1,977
- Community control participants: 640
- 12-30 years of age
- 43 sites



ProNET: Psychosis-Risk Outcomes Network


Scott Woods
Yale University

Carrie Bearden
University of California, Los Angeles

John Kane
Northwell Health

DPACC: Data Platform with Data Processing, Analysis, & Coordination Center

Martha Shenton
Harvard University

Rene Kahn
Icahn School of Medicine at Mount Sinai

PRESCIENT: Trajectories and Predictors in the Clinical High-Risk for Psychosis Population

Barnaby Nelson
University of Melbourne

Patrick McGorry
University of Melbourne

Data Rigor/SOPs for the Observational Study

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

PSYCHS - Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS

* In- person visit

Observational Study: Recruitment and Data Releases

Recruitment Sites

43 sites across North America, South America, Europe, and Asia

Target: 1,977 CHR
640 HC

3,515 participants started baseline

1,946 participants started month 2 timepoint

1,218 participants started month 6 timepoint

676 participants started month 12 timepoint

61 participants converted to psychosis

Recruitment

Curated Data Release

- Curated data releases every six month NIMH Data Archive
  - Data Release 1.0
  - Data Release 2.0
  - Data Release 3.0 by March 2025

Digital Assessment in AMP® Schizophrenia

Digital Measures have the potential to provide signals that:

- can be collected in **naturalistic contexts** while young people live their lives
- are sensitive to **within-person functional change**

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Conversion
Month	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	18	24	-
Consent Form																	
Brief Psychiatric Rating Scale																	
Actigraphy (daily)																	
Digital Data (daily passive sensing, EMA, audio diary)																	

- **12-months of digital assessments** (Phone + Wearable) for CHR and Healthy Controls
- **Monthly Digital Check-Ins** with research staff coincide with structured clinical assessments

Internal Data Quality Monitoring Procedures

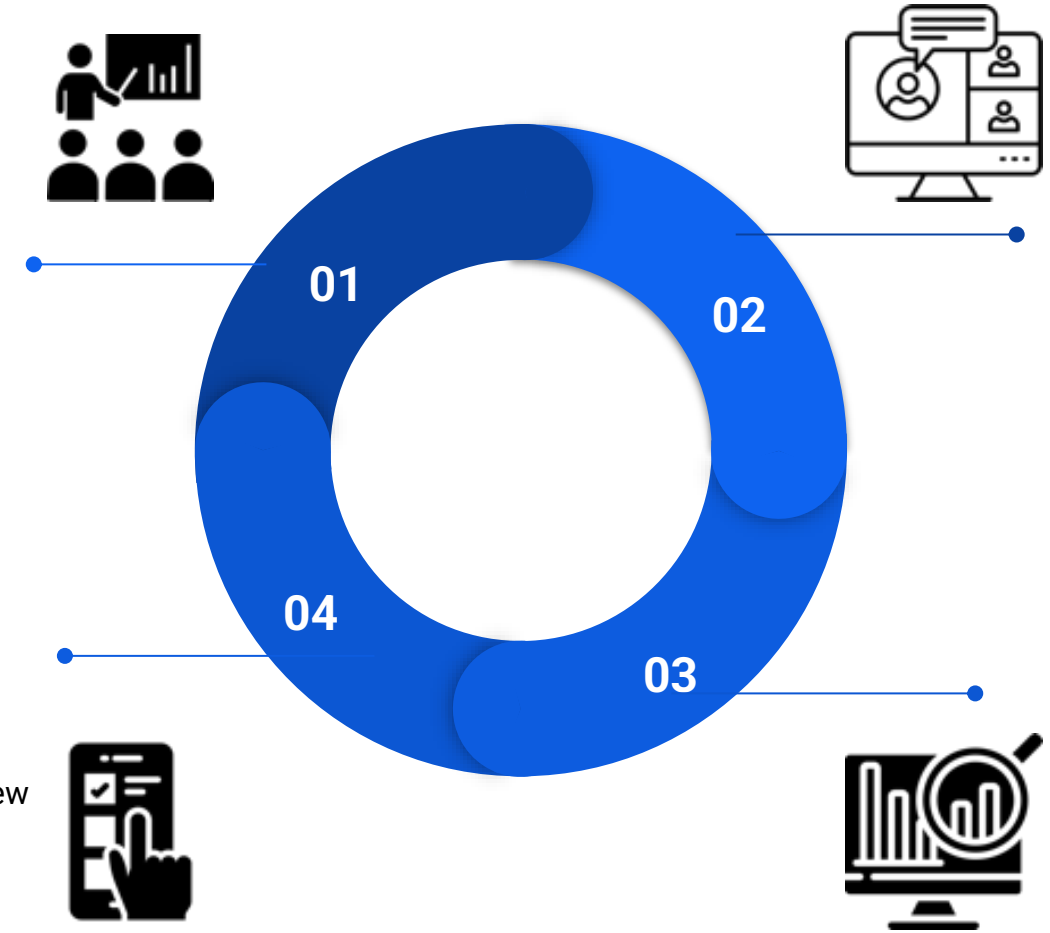
Initial Training

Initial 8-10 hour training in troubleshooting, mindLAMP and data interpretation

Ongoing (Weekly or Monthly) Additional Feedback

Staff review active and passive data quality per data quality visualizations.

Staff meet participants and review weekly data quality.



Participant Introduction

Standard onboarding per AMP SCZ SOP

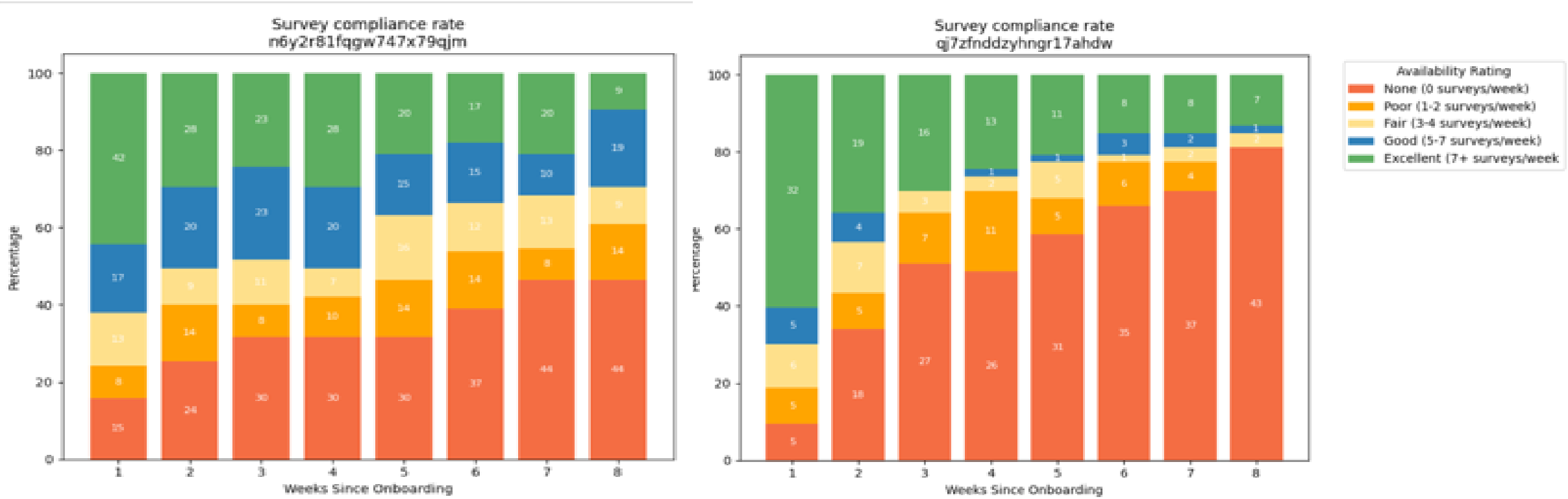
Continuous Data Quality Report Collected

mindLAMP's dashboard automatically displays daily survey completion

mindLAMP is equipped to automatically generate data quality reports illustrating hourly data quality

Justin Baker, MD, PhD and John Torous, MD, MBI

Goal: Avoid variation in engagement between sites



Variation in EMA survey engagement between two selected sites shown above

Four step approach used to minimize such variation in engagement

Justin Baker, MD, PhD and John Torous, MD, MBI

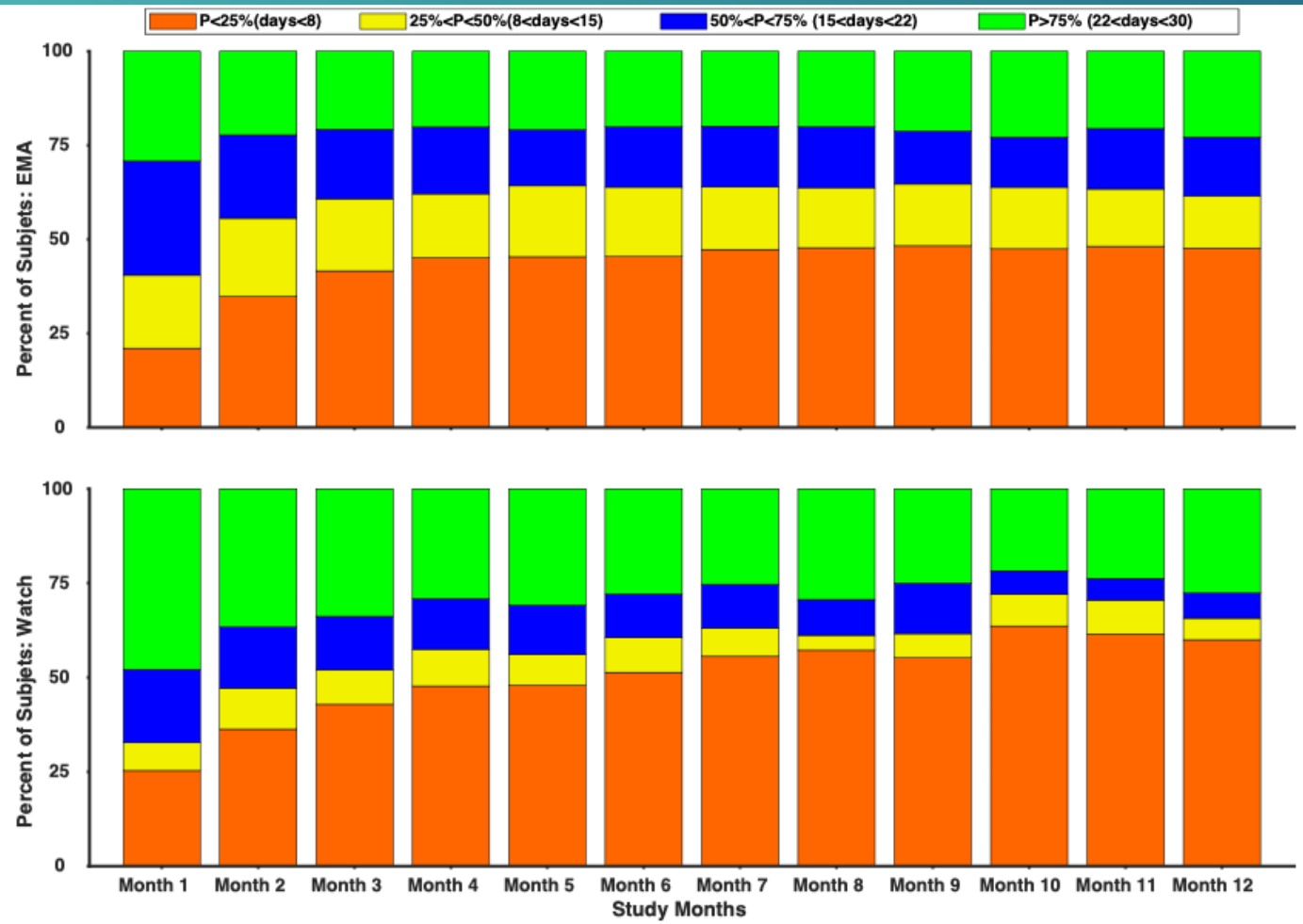
Digital Biomarker Adherence (over 12 months)

Phone EMA Data

Number of Subjects: 1614

Watch Actigraphy Data

Number of Subjects: 648



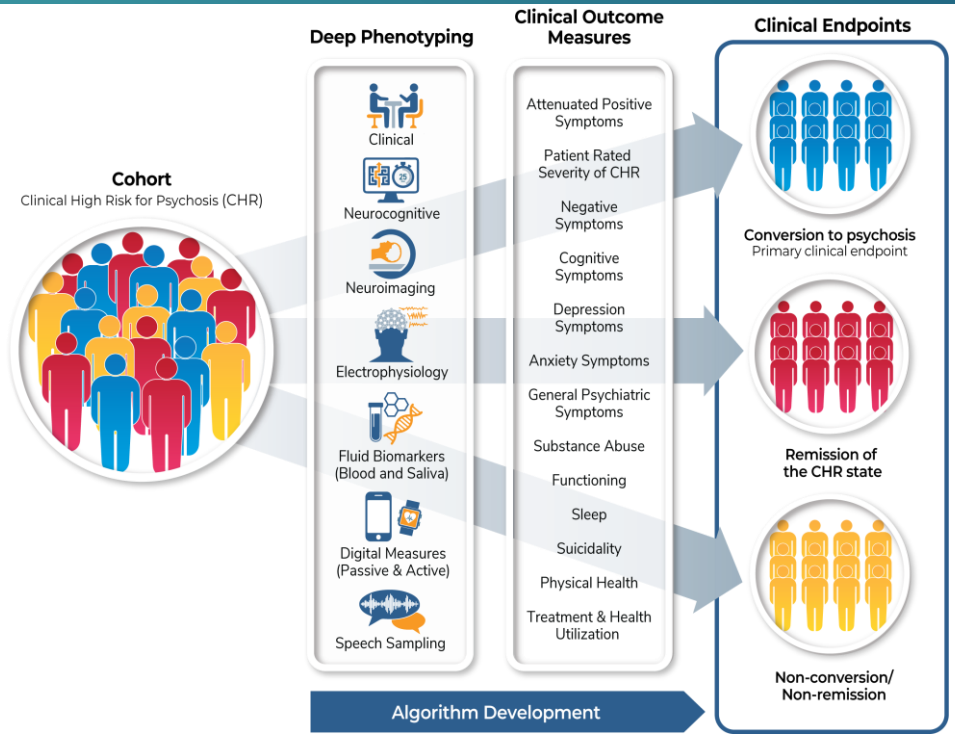
Justin Baker, MD, PhD
John Torous, MD, MBI

Justin Baker, MD, PhD and John Torous, MD, MBI

Analysis Aims of AMP SCZ

- **Primary aim:** Using a set of baseline clinical assessments and multi-modal biomarkers to predict clinical endpoints of CHR individuals
  - "Baseline data" includes screening until month 2.
  - Prediction of the **three endpoints** (conversion, remission, non-conversion/non-remission) at **Month 12**, Month 24

- **Secondary aim:** Using the longitudinal clinical assessments and multi-modal biomarkers from all time points to characterize clinical trajectories of CHR individuals
  - Input is information from all modalities and all time points
  - Search for sub-types/clusters that are of clinical importance or that provide improved mechanistic understanding
  - Enables searching for other outcome measures that might be associated with the endpoints and could be used as alternative endpoints in future trials



Overarching goals: developing tools that identify the early stages of risk for schizophrenia, and that can identify new targets for drug-based treatments that can be tested in clinical trials

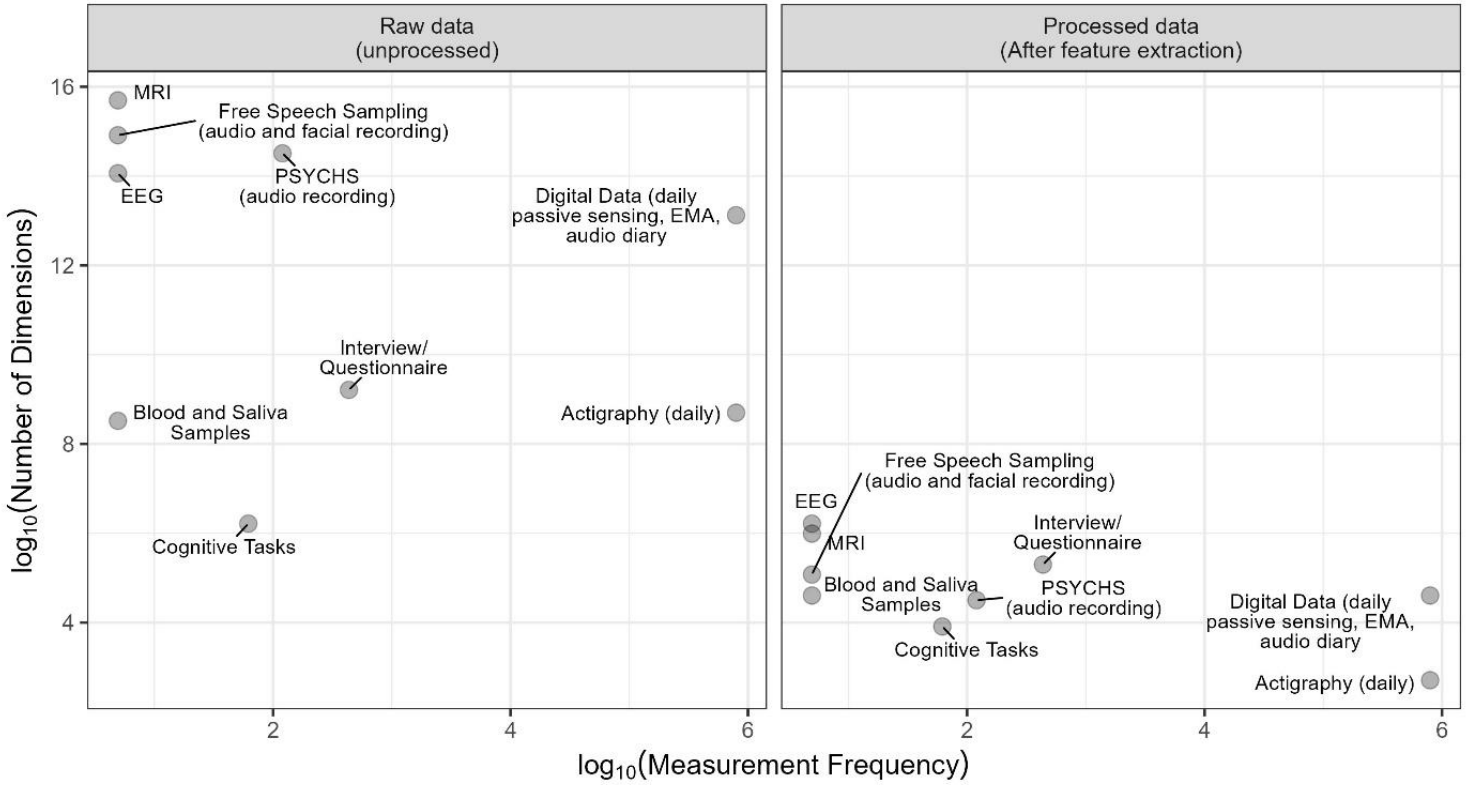
Feature engineering

AMP SCZ domains have vastly variable dimensions and frequency

The high number of assessments produces a large number of features with different relevance that require feature engineering for dimensionality reduction

Approaches for feature reduction:

- Hypothesis driven/Expert based selection
  - Driven by workgroups for each domain
- Composite scores
  - e.g., interview-based and cognitive data
- Data driven analytical dimensionality reduction
  - e.g., Principal Component Analysis (PCA) Multidimensional Scaling (MDS), Elastic Net
- Wrapper-based feature selection
  - Optimization is performed while individual features are added or removed consecutively to the feature space



Combining predictive modeling across multiple modalities– Data fusion techniques

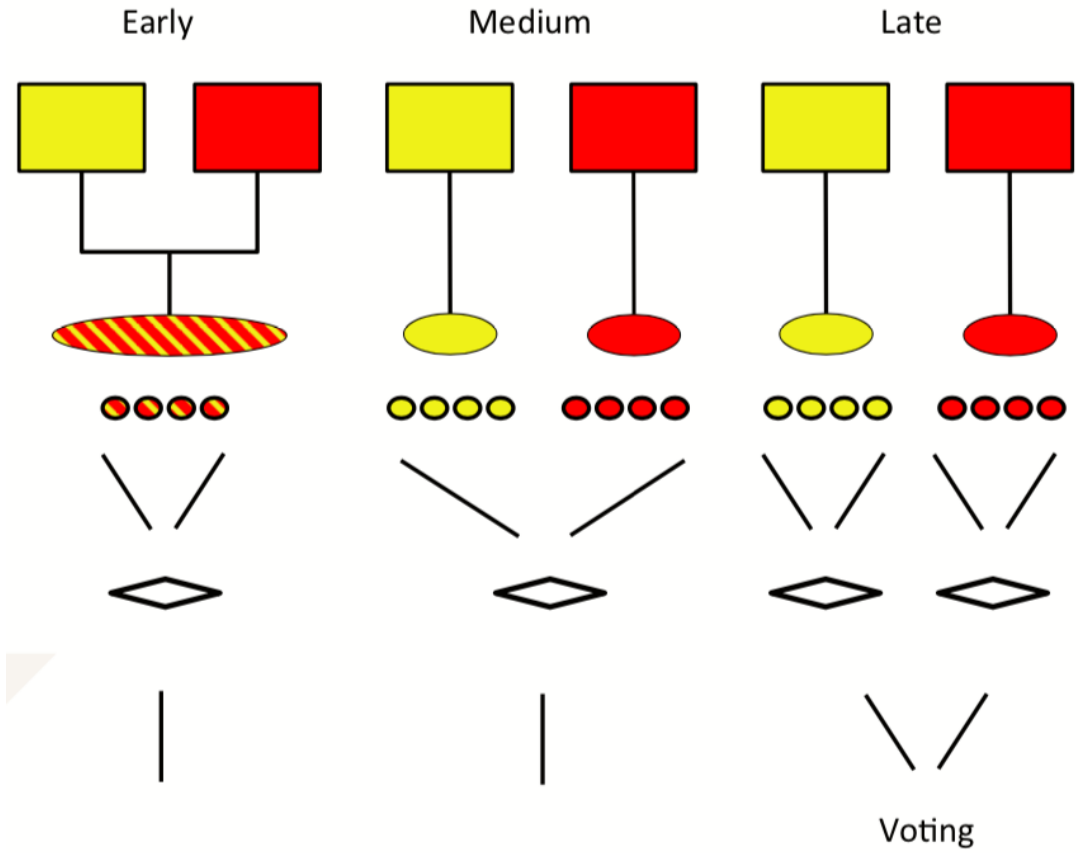
- **Definition:**
  - Data for AMP SCZ is composed of multiple domains, each with its own derived features and outcome measures.
  - Leveraging the richness of data requires fusion techniques for combining data to make a prediction.

- **Early Fusion:**
  - All features from all modalities in one big bag of features.
  - Limitations: Too high dimensionality; Ignores distinctions between modalities; biased towards modality with more features.

- **Late Fusion:**
  - Separately train a model for each modality. Then uses a voting mechanism to make a final prediction.
  - Limitations: Interactions between modalities are not reflected.

- **Intermediate Fusion:**
  - Use intermediate layers to separately derive prediction variables from each modality. Then create a model that combines these variables across modalities.

  - Intermediate dimensionality between Early and Late fusion.
  - Can capture associations between modalities.



AMP SCZ will follow the IP and data sharing policies established for AMP initiatives

- Research supported by AMP is precompetitive
- Data is shared broadly; AMP participant partner organizations may have access to data during assessment of data quality control
- No pre-emptive patenting to ensure broadest possible opportunity for commercialization

AMP SCZ PSYCHS Instrument and Standard Operating Procedures

PSYCHS Instrument (Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS), Interview Manual and Training Materials are posted on Zenodo

The Clinical, Cognitive, MRI, Language, Fluid Biomarkers, EEG, Actigraphy, and EMA and Passive Sensing are posted on Zenodo and linked to the AMP SCZ website

https://www.ampscz.org/scientists/sops/

Schizophrenia (formerly NPJ Schizophrenia): 10 methods papers are in the final stages of revisions and will be included in a special edition of Schizophrenia

- MRI, EEG, Cognition, Digital Biomarkers, Language, Fluid Biomarkers
- Data Flow, Dissemination & Lived Experience, Data Analysis
- Clinical

Tools of Interest, Development, and Use

PSYCHS is the main tool of interest as a COA for APSs to determine the clinical endpoints for future CHR clinical trials

- The observational study will collect psychometric data on the use of PSYCHS to assess APSs in CHR
- Data collected for PSYCHS will lay the framework for subsequent validation studies
- The daily digital data and repeated cognitive and clinical measures collected at months 3-4 months will be useful for identifying tools and measures that could be used to detect clinical change over time with an intervention in a short-term clinical trial

Proof of Principle (PoP) Trials: What we anticipate learning

Deliverables

Utility of clinical outcomes (e.g., PSYCHS instrument) and biological measures.

Ability to detect a change in signal using biological, cognitive, digital, or clinical outcome measurement within a 12 to 16-week study period.

Study design informed by data from ongoing observational study and informal feedback from FDA.

Ability to conduct biomarker-based studies of novel interventions in the CHR population to de-risk a path for therapeutics development.

AMP SCZ Partners

Public Sector

NIH National Institute of Mental Health

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ex-Officio

FNIH

Private Sector

Boehringer Ingelheim

Johnson&Johnson Innovative Medicine

Otsuka

AMERICAN PSYCHIATRIC ASSOCIATION FOUNDATION

NAMI
National Alliance on Mental Illness

ONE MIND

Schizophrenia & Psychosis Action Alliance

wellcome