

Qualification Plan for PSYCHS as a ClinRO for Patients at Clinical High Risk for Psychosis

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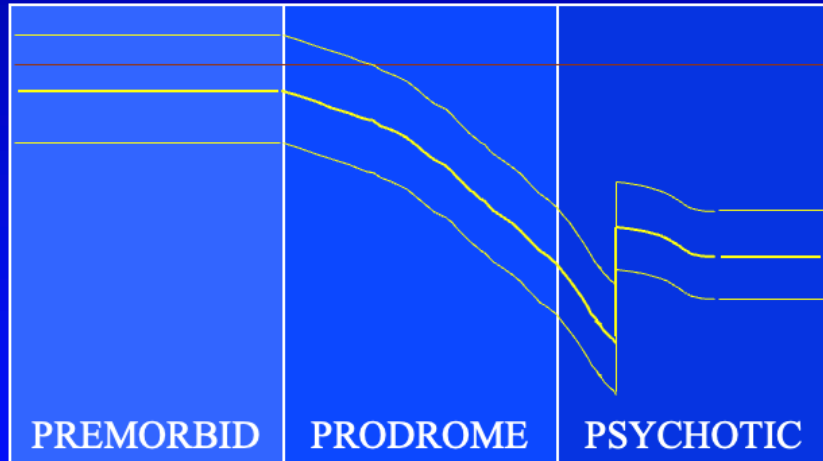


Disclosure

Dr. Woods has received speaking fees from the American Psychiatric Association and from Medscape Features. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. He is a consultant to and is a partner and owns stock in NW PharmaTech.

THE CLINICAL HIGH RISK SYNDROME FOR PSYCHOSIS

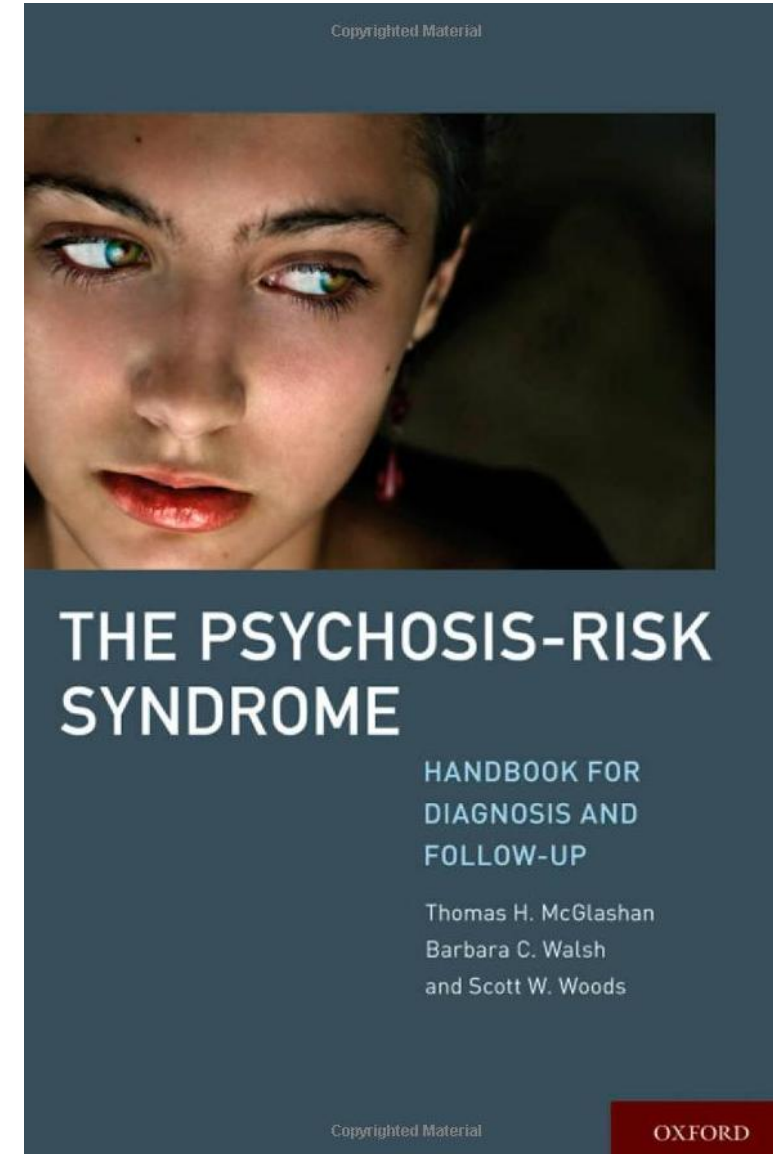
PHASES OF PSYCHOSIS



Course of Illness

- CHR is NOT an asymptomatic risk factor.
- The patients are youth and young adults identified by subsyndromal or “attenuated” positive symptoms resembling those in schizophrenia.

- Schizophrenia is one of the top 15 most disabling illnesses.
- >75% experience a prodrome prior to onset (Benrimoh et al 2023).
- CHR identifies the SCZ prodrome prospectively.



Case of Angus

Angus, a single, 22-year-old Caucasian male, attended college full-time. He came from an intact family For **the past eight months** he had become **increasingly concerned about an image he sensed near him** whenever he was in the bathroom of his apartment washing his face or showering.

The image was that of **a shadowy, vaguely female figure**, whose presence was triggered by running water. He was frightened by the image and felt she was **“spiteful” and wished that he would die** by falling in the bathroom. Angus **knew that it was not real, but it bothered him**. The image appeared almost every time he entered the bathroom, so he avoided showering and washed only half his face at a time.

More about Angus

Angus acknowledged that his friends regarded him as “weird” because of his preoccupation with themes such as the moral **messages hidden in the music** he played, **the decline of civilization**, and the **special meanings** he obtained **from** games of **chess**. He felt unmotivated, had subtle difficulty completing his homework despite maintaining high grade point average, and procrastinated on his personal activities of daily living. He needed frequent prompts from his roommate to get up, out of bed or go to class.

He felt confusion once or twice a month, during which time he forgot what he was talking about in midsentence, and his friends noticed this. In fact, his girlfriend frequently complained to him that he was not the same. Angus also worried that **other students wanted to exclude him** from certain social groups, although **he believed that he was probably imagining this**. He complained of feeling unmotivated and different from how he felt when he was younger.

SUBSTANTIAL UNMET CLINICAL NEED IN CHR

- **Identifiable** with high reliability and validity based on attenuated positive symptoms (Woods et al 2019).
- No unique billing code, but listed in DSM-5 among three other disorders under 298.8. DSM-5 recommends ICD-10 F28.
- **Common:** Point prevalence at 1.7% of the general youth population and 19.2% of the population of youth presenting for psychiatric care (Salazar de Pablo et al 2021).
- **Impairment:** Typically distressed by symptoms and show moderate functional impairment.
- Cognitive deficits on average (Seidman et al 2016).
- Affective and anxiety symptoms and comorbid diagnoses.
- ~20% eventually convert to syndromal psychosis (Fusar-Poli et al 2020), on average in 1-2 years (Powers et al 2020).
- Patients who do not convert often have ongoing symptoms and impairment (Addington et al 2019).
- **Being treated:** More than 100 CHR specialty clinics in multiple countries on six continents (Kotlicka-Antczak et al 2020). An additional ~35 CHR clinics in the US funded by SAMHSA.
- No approved pharmacologic therapies.

Development of the PSYCHS: Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS

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Abstract

Aim: To harmonize two ascertainment and severity rating instruments commonly used for the clinical high risk syndrome for psychosis (CHR-P): the Structured

Individual names of AMP SCZ collaborators are listed in the Acknowledgment.

Accelerating Medicines Partnership Schizophrenia (AMP SCZ) authors are listed in the section Appendix A.

For affiliations refer to page 12.

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PSYCHS Roles in Drug Development

1. Ascertainment

- a. Excludes frank psychosis
 - b. Includes CAARMS CHR
 - c. Includes SIPS CHR
- } Context of Use (COU)

2. Clinical Outcome Assessment (COA)

- a. Attenuated positive symptom severity defined by:
 - i. PSYCHS severity scale (15 items, each rated 0-6, highest over past 4 weeks)
 - ii. SIPS
 - iii. CAARMS
- b. Conversion to psychosis
- c. Remission from CHR

Used in the Accelerating Medicines Partnership® Schizophrenia

- CHR Observational Study
- CHR Proof-of-Principle Trials

Example of a PSYCHS Item

P1 - Unusual Thoughts and Experiences

Inquiry 1 - Unusual Thoughts and Experiences

1. *Have you ever had the feeling that something odd is going on or that something is wrong?*

* must provide value

Yes
 No

reset

Inquiry 1 - Unusual Thoughts and Experiences

1. *Have you ever had the feeling that something odd is going on or that something is wrong?*

* must provide value

Yes
 No

reset

Ask as many of these as necessary to be confident of your rating:

- Can you tell me more about it?
- What was it like?
- Can you give me an example?
- What did you make of it?
- How did you explain it?
- How sure were you that it really happened?

Cover these domains whenever a bolded symptom inquiry is endorsed unless you are confident the rating is 0:

- How did it make you feel?
- Did it bother you?
- Did you do anything differently because of it?
- When did it start?
- Did it stop? When?
- How often did it happen?
- When it was there, how long did it last?

* must provide value

Rate the highest experienced over the past 4 weeks.

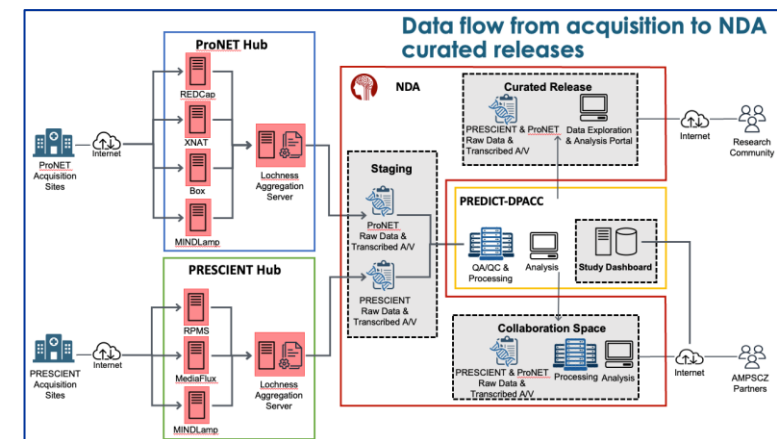
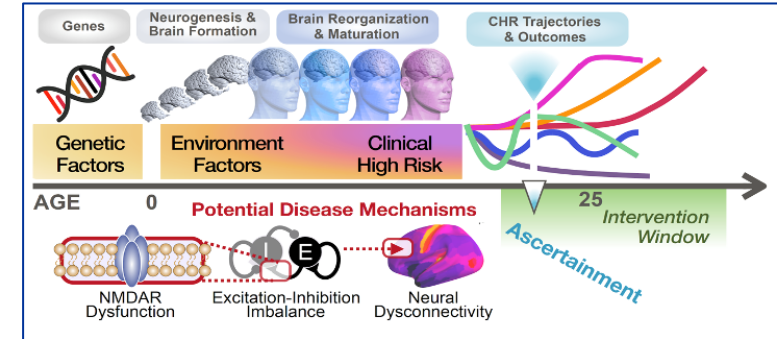
CONCEPT/ SEVERITY	0 Absent	1 Questionable	2 Mild	3 Moderate	4 Marked	5 Severe but Not Psychotic	6 Psychotic and Very Severe
DESCRIPTION	No unusual thought content.	Unusual thoughts or experiences such as deja vu or other "mind tricks" that occur not uncommonly in the general population.	Unusual thoughts or experiences such as over interest in fantasy life or unusually valued ideas/ beliefs or superstitions. Feeling of unease in absence of reason or cause that person can identify. Premonitions. Beliefs beyond what would be expected of the average person but within cultural norms.	Unusual thoughts or experiences such as ideas/ mental events that are meaningful, puzzling, unwilled, and not easily ignored. Sense that something is different or not quite right or that things are different with the world. Seems to the person most likely imaginary.	Unusual thoughts or experiences such as unlikely or referential ideas/mental events with the sense that they may be real.	Unusual thoughts or experiences such as peculiar or improbable ideas/ mental events that seem real.	Unusual thoughts or experiences such as strange and/or highly improbable ideas/ mental events that feel completely real.

Symptom tenacity and distress and interference due to the symptom are also rated 0-6. An algorithm calculates the overall severity score for that item.

AMP® SCZ LAUNCHED IN JUNE 2022 AFTER A 12-MONTH PLANNING EFFORT LED BY THE FOUNDATION FOR NIH



- The overall aim of the AMP SCZ **Observational Study** is to provide tools to parse heterogeneity and improve success in developing pharmacologic treatments for patients with CHR for psychosis.
- Three grants: ProNET, PRESCIENT, PREDICT DPACC, including 43 sites on 5 continents.
- **Met and surpassed recruitment goals: 2034 CHR and 652 HC to be followed over 2 years.**
- MRI, EEG, fluids, digital, and language biomarkers.
- Data deposited in NIMH Data Archive.
- 3 Public sector partners. Private partners include: 3 non-profit partners, 2 private foundations, and 3 industry partners.

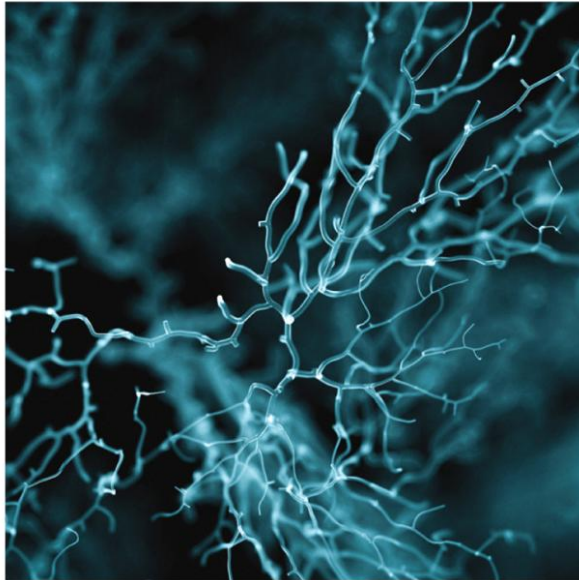


Courtesy Alan Anticevic

Courtesy AMP SCZ

Courtesy PREDICT DPACC

AMP® SCZ Proof-of-Principle Trials Launched in February 2026



People

Pipeline

Publications

News

Blogs

Contact

Monument Therapeutics Announces Partnership with Foundation for the National Institutes of Health for Clinical Trial of MT1988, a Novel Treatment for Schizophrenia

August 19, 2025

AMP SCZ: <https://fnih.org/our-programs/accelerating-medicines-partnership-amp/amp-schizophrenia/>
MT: <https://monumenttx.com/news/>

Clinical Outcome Assessment (COA) Qualification

1. Advantage

- a. When submitting an IND, a Sponsor can rely on FDA approving the primary endpoint for the approved COU
- b. De-risks the IND submission

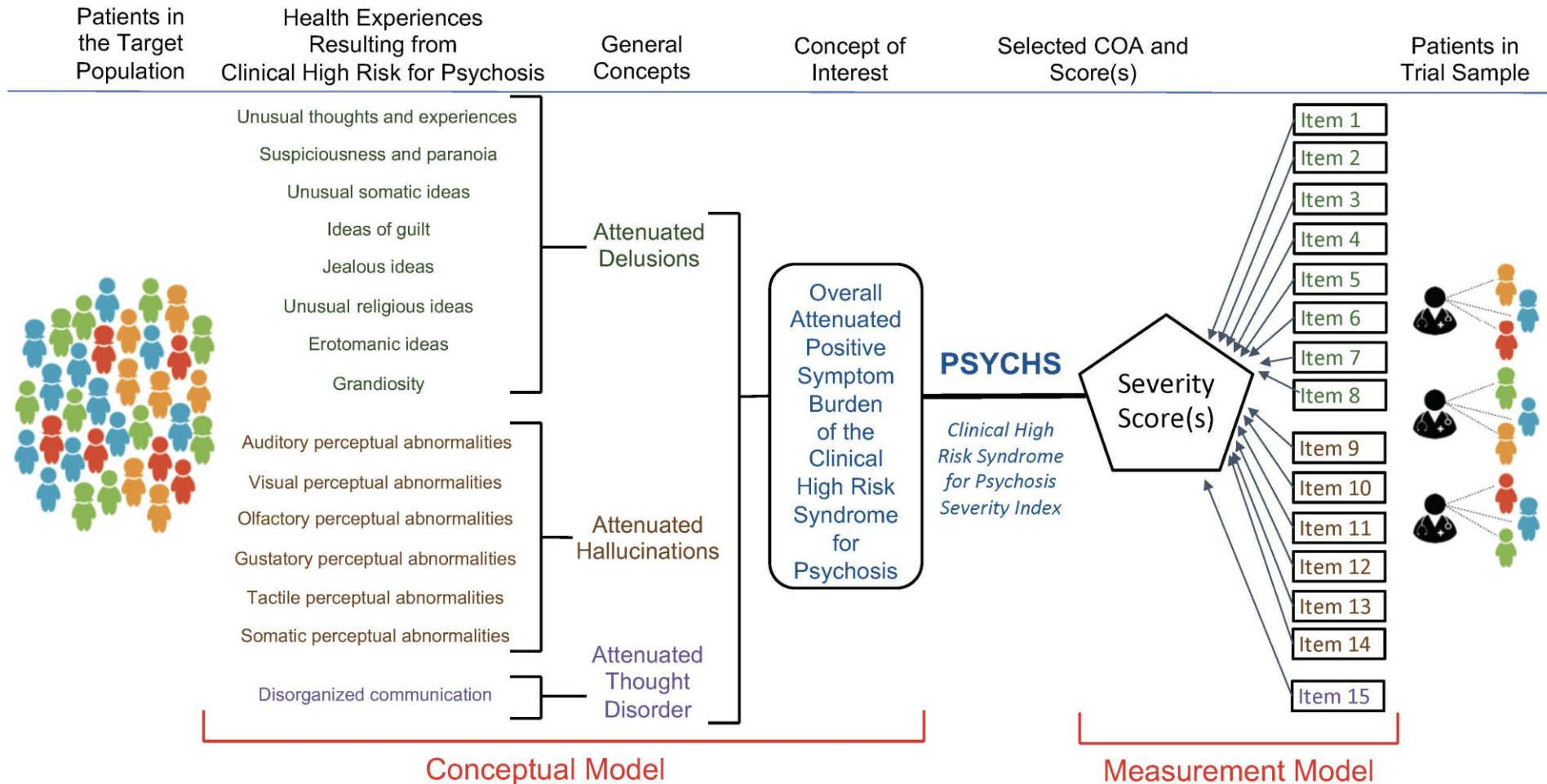
2. Qualification Process and PSYCHS progress

- a. Stage 1: Letter of Intent – LOI 000163 accepted
- b. Stage 2: Qualification Plan – hoping to submit Q2 2026
- c. Stage 3: Full Qualification Package

Key Elements of A Qualification Plan

- Content Validity
 - Concept saturation
 - Usability testing
 - Item selection
 - Recall period
 - Conceptual framework
- Measurement Properties
 - Test-retest reliability,
 - Construct validity
 - Inter-rater reliability
 - Missing data simulation
 - Instrument
 - Manual
 - Ability to detect change
 - Meaningful within person change
 - Criterion validity

Conceptual Framework of the PSYCHS



Concept Saturation Qualitative Interviews

These interviews explore participants' health experiences, including how distressing or impairing they are in daily life.

- Methods are in progress.
- Participant interviews are transcribed verbatim. For example: “I also sometimes have a hard time processing time... not fully understanding... the way that time passes.”
- Once methods are final, the elicited concept might be “Impaired time perception.”
- Determine whether the elicited concept is attenuated positive symptom content.
- Determine whether the elicited concept is captured in one of the PSYCHS items. For example: PSYCHS Item P1 Inquiry 4

Inquiry 4 - Unusual Thoughts and Experiences

4. Has your experience of time ever seemed to have changed? Has it become unnaturally faster or unnaturally slower?

* must provide value

Yes

No



reset

- Summarize results using a saturation table.

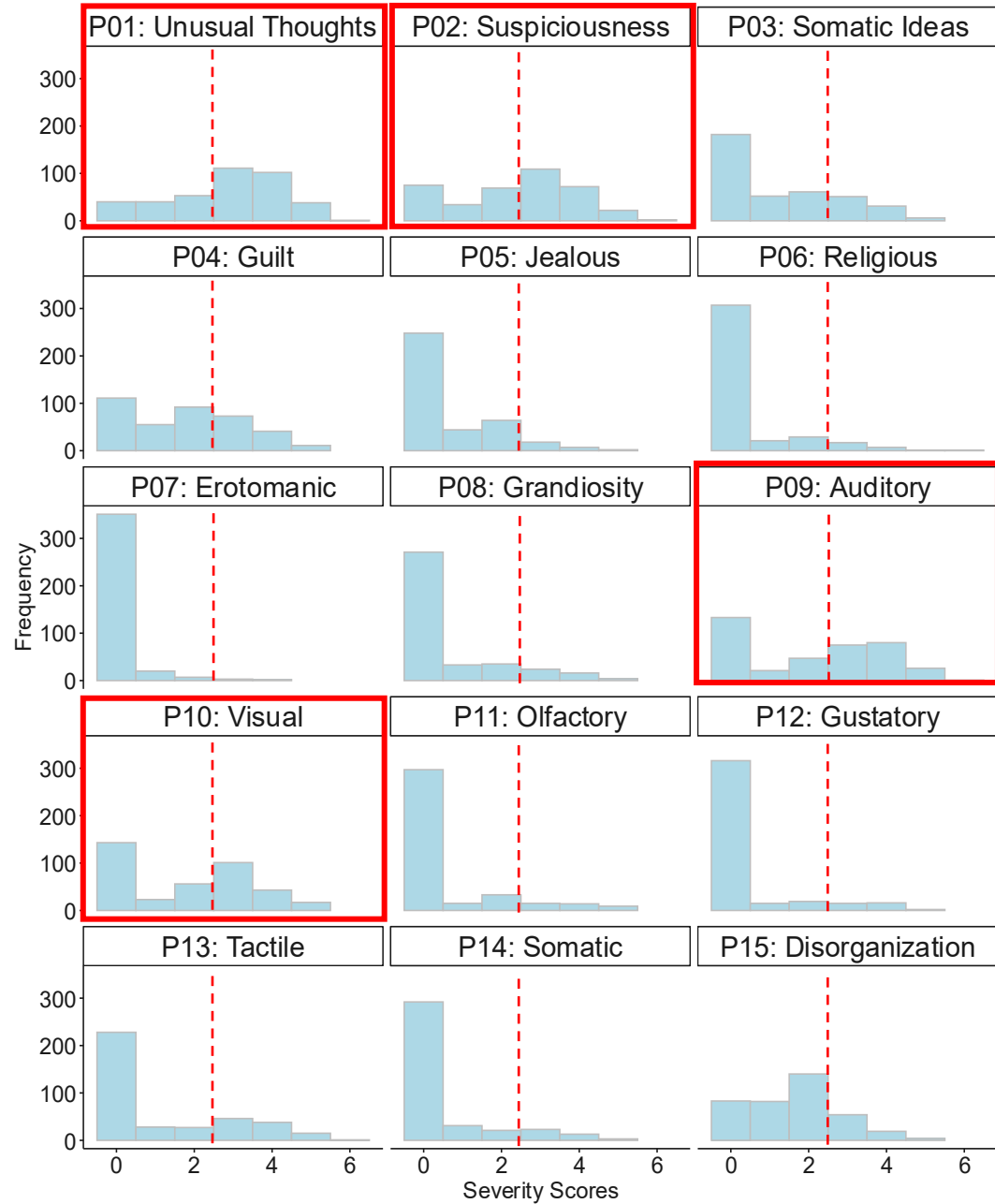
Usability Testing Cognitive Interviews

The aim of these interviews is to evaluate participant's understanding of PSYCHS inquiries

	Original Inquiry	Cognitive Interview Probe(s)	Participant Response	Issues Identified		
				Issue 1	Issue 2	Issue 3
	Have you ever had the feeling that something odd is going on, or that something is wrong?	Can you tell me what that means in your own words? / What is an example of something that might make you say yes, like what kind of thing might happen, where you would say, yeah, I've had that feeling that something off is going on.	Put in my own words what I think that anything strange is happening./ Would be referring to believing that something paranormal was happening.			
S1	Have you ever been confused at times whether something you have experienced is real or imaginary?	Can you tell me what that means in your own words?/ Can you give me an example?	That could mean if you've ever questioned your own reality. / Maybe someone's questioning whether or not the person they met earlier was even real, or maybe they are questioning whether or not they imagine the conversation they had.			
	Have you ever daydreamed a lot or found yourself preoccupied with stories, fantasies, or ideas?	Can you tell me what that means in your own words?/ how would you describe a daydream?	That could be someone having like maladaptive daydreams. Yeah, they just space out a lot. A very vivid imagination. Not just the thought, but it's almost like a someone took a lot of effort to dream up a scenario, and being in a world that they created.			
	Have you ever had the feeling that something odd is going on, or that something is wrong?	Can you tell me what that means in your own words?	A thing changed, or something unusual happened without any rational external cues. I would feel like something weird is going on.			
S2	Have you ever been confused at times whether something you have experienced is real or imaginary?	Can you tell me what that means in your own words?	I think it's pretty explicit. I my rephrase was exactly like the question asking, Yeah, it's like, Am I? Am I experiencing the reality and maybe I living on some, maybe I living. world, that nothing is real or what I'm experiencing is actually objectively happen.			
	Have you ever daydreamed a lot or found yourself preoccupied with stories, fantasies, or ideas?	Can you tell me what that means in your own words?/ What does daydreamed mean to you?	How often I'm mind wandering, or think about other stuff that's not related to the task I'm currently supposed to work on. / [I] think a lot of things that is not real, or plan for the future, or think about the past, or think about some fantasies or some unrealistic stuff.			

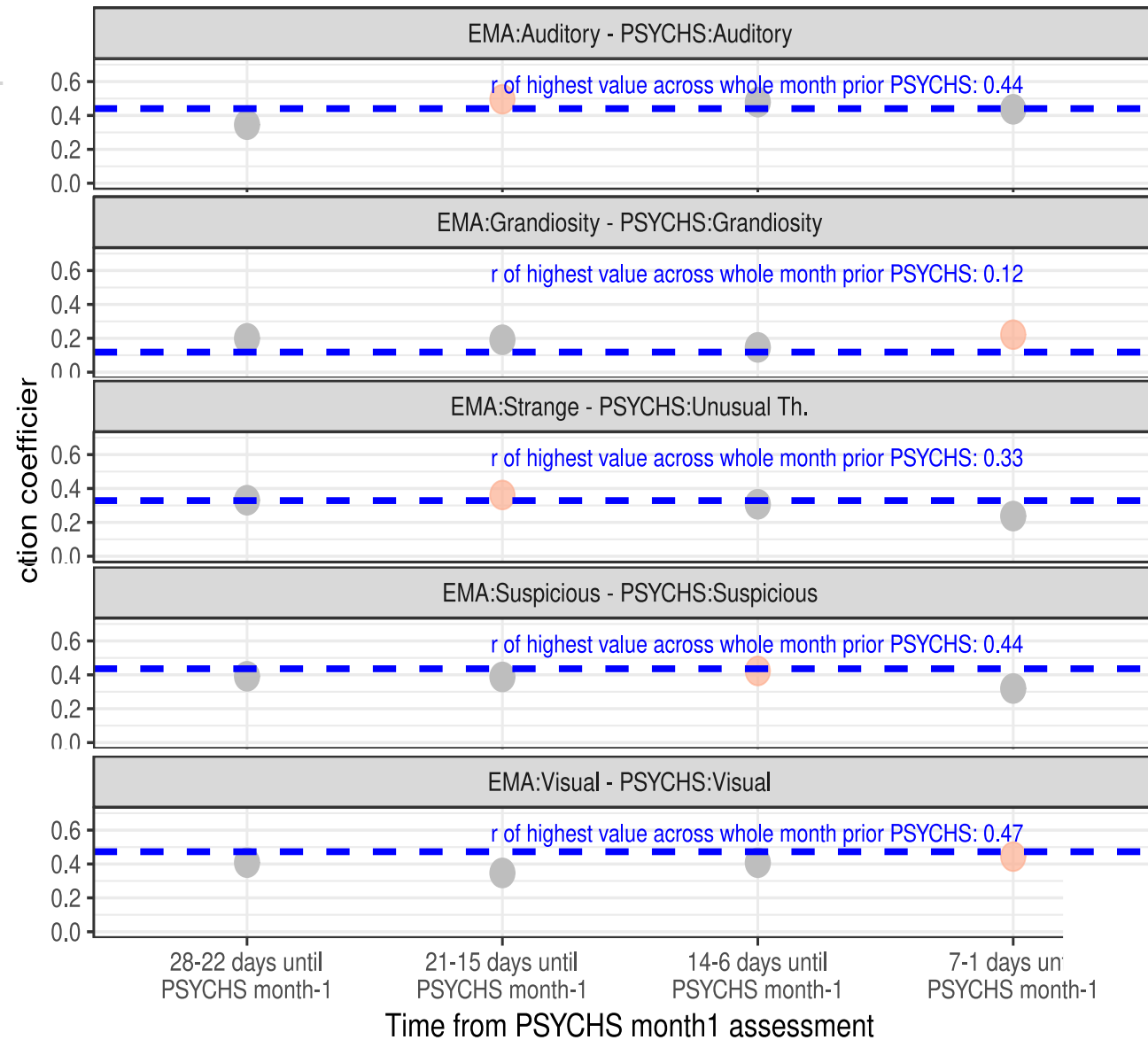
Item Selection

Severity



Distribution

Recall Period – Is four weeks too long?



Instrument and Manual

- PSYCHS Screening Version used for ascertainment.
 - Administration time typically 60-90 minutes.
- PSYCHS Follow-up Version used at baseline and subsequently at four-weekly intervals.
 - Administration time typically 30-45 minutes.
- Intended for direct use in an EDC.
- Currently implemented in REDCap.
- Highly adaptive, making extensive use of calculations and branching logic.
- For display in the Qualification Plan, making extensive use of screenshots showing how the calculations and branching logic work for the interviewer.
- Will be posted on ampscz.org.

Construct Validity: Convergent and Divergent

Convergent Validity against the BPRS

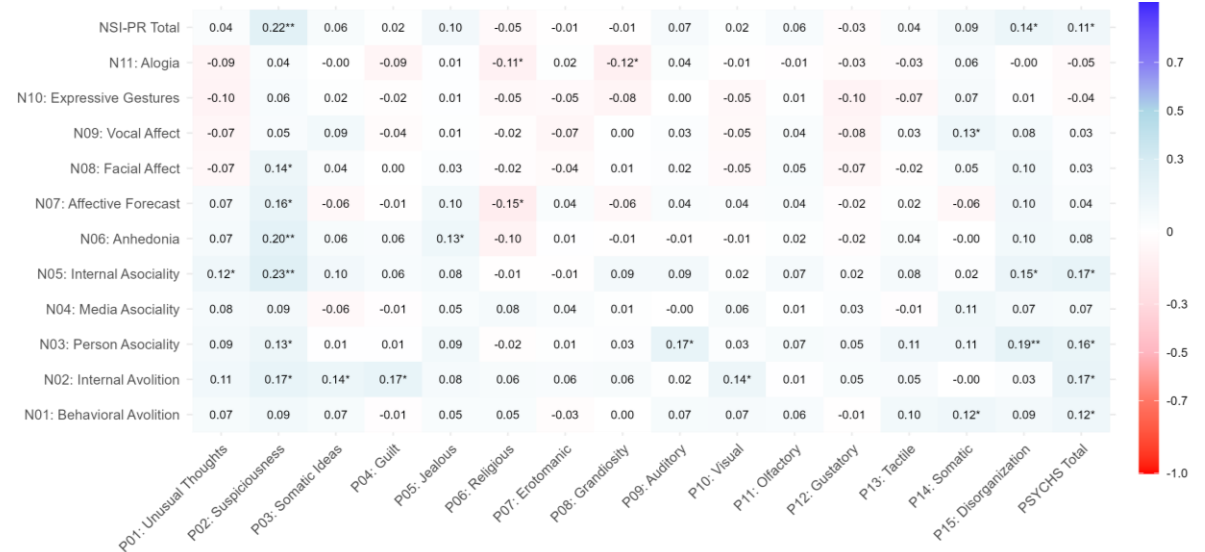


Data from AMP SCZ Observational Study, 2nd Release

Divergent Validity against Anxiety and Depression



Divergent Validity against Negative Symptoms



Sensitivity to Change in Two Published Clinical Trials Using SIPS and PANSS in CHR

Change from baseline to one year (LOCF), McGlashan et al 2006 doi.org/10.1176/ajp.2006.163.5.790									
			<i>SIPS positive</i>				<i>PANSS positive</i>		
		n	mean	sd	Cohen's d		mean	sd	Cohen's d
	Olanzapine	30	-3.50	5.78	0.57		-1.63	5.65	0.40
	Placebo	29	0.31	7.60			0.86	6.74	
Percent change from baseline to ten weeks, Kim et al 2011 doi:10.1111/j.1751-7893.2011.00267									
			<i>SIPS positive</i>				<i>PANSS positive</i>		
		n	mean	sd	Cohen's d		mean	sd	Cohen's d
	CBT	18	-40.9	nr	1.46		-30.2	nr	1.34

The first AMP SCZ PoP study will also be useful in determining whether the PSYCHS or the PANSS shows a greater effect size.

Clinically Meaningful Change in PSYCHS at 12 Weeks for Endpoint Analysis

A decrease of 5 points in the overall PSYCHS severity score indicates a clinically meaningful change when analyzed against the Patient Global Impression and the overall BPRS score.

Table 1. Distribution of PSYCHS Total Score Change-From-Baseline Scores at 12 Weeks for AMP SCZ CHR Patients With a 1-Category Improvement in Patient Global Impression of Severity. Negative values indicate improvement.

PGI-S at Baseline	N (%)	Change in PSYCHS Total Score from Baseline to 12 Weeks				
		10 th Percentile	25 th Percentile	50 th Percentile	75 th Percentile	90 th Percentile
<i>Mild</i>	14 (28.5)	0.4	-2.5	-6.5	-8	-12.2
<i>Moderate</i>	28 (57.1)	1	-2.5	-5.0	-9	-11.5
<i>Severe</i>	7 (14.7)	2.8	0	-8.0	-11.5	-13.4

The PGI-S is a single-item PRO for CHR whose content is related to, but not a direct reflection of, the severity of attenuated positive symptoms : "Please choose the response that best describes the overall severity of your mental health symptoms over the past 7 days." Its recall period is 7 days, while the PSYCHS recall period is the highest severity over the past month.

Table 2. Distribution of PSYCHS Total Score Change-From-Baseline Scores at 12 Weeks for AMP SCZ CHR Patients With an 8-12 Point Improvement in BPRS-total. Negative values indicate improvement

BPRS total at Baseline	N (%)	Change in PSYCHS Total Score from Baseline to 12 Weeks				
		10 th Percentile	25 th Percentile	50 th Percentile	75 th Percentile	90 th Percentile
<i>Tertile 1 (34-38)</i>	8 (33.3)	-13.30	-10.0	-6.0	-2.25	0.3
<i>Tertile 2 (39-41)</i>	9 (37.5)	-14.2	-10.0	-5.0	-4.0	-0.4
<i>Tertile 3 (43-51)</i>	7 (29.2)	-10.4	-6.5	-4.0	2.0	6.4

Figure 2. Change-From-Baseline Scores at 12 Weeks, N=231

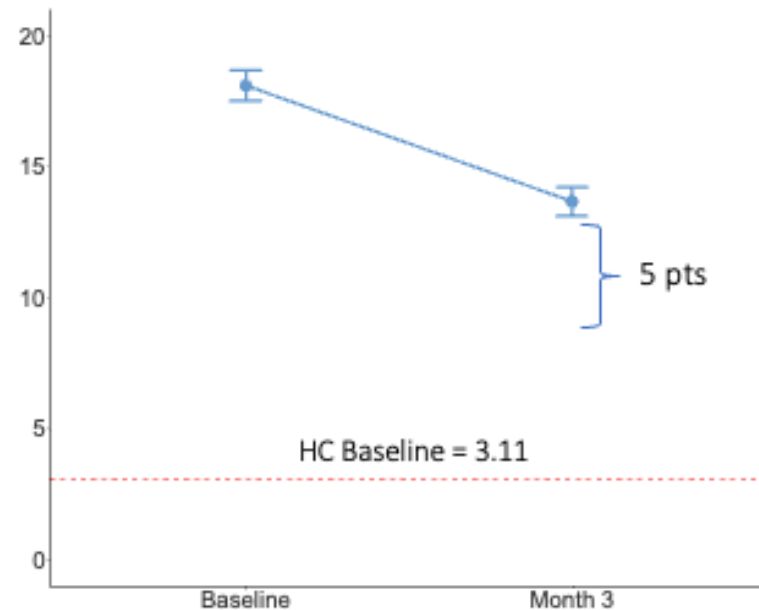


Table 3. Descriptives Total PSYCHS severity scores at Baseline and 12 weeks follow up.

	Mean	Sd	Median	Min	Max
Baseline	18.1	8.88	17	0	43
Month 3	13.7	8.27	13	0	39

Criterion Validity

Design

Current Recruitment

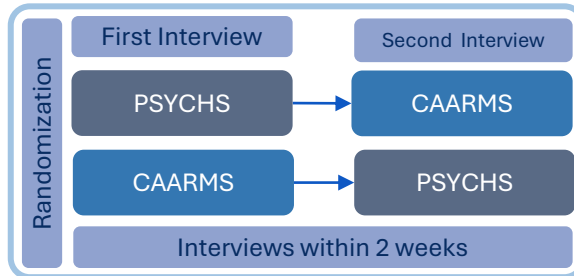
Preliminary results Study 2

Study 1

40 CHR

40 non-CHR or PSY

20 Psychotic



Group	Female	Male	Total
CHR	16	8	24
Psychosis	2	0	2
Neither	7	7	14
Total	25	15	40

Absolute agreement in ascertainment SIPS and PSYCHS

		PSYCHS (n= 20)		
		Neither	CHR	Psychosis
SIPS	Neither	5	0	0
	CHR	0	9	1
	Psychosis	0	1	4

Kappa = 0.842, 95%CI (0.657 -1.00)

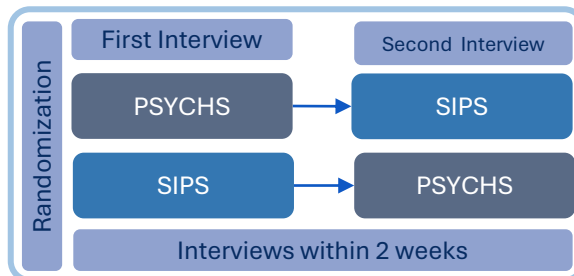
Median kappa for IRR 0.89, 16 samples, Woods 2019

Study 2

40 CHR

40 non-CHR or PSY

20 Psychotic



Group	Female	Male	Total
CHR	16	5	21
Psychosis	3	3	6
Neither	4	1	5
Total	22	9	31

Item level agreement SIPS and PSYCHS

Item	ICC(1)	95% CI
P1 Unusual Thoughts (PSYCHS P1, P3, P4, P5, P6)	0.932	0.860 - 0.971
P2 Suspiciousness (PSYCHS P2)	0.896	0.787- 0.954
P3 Grandiosity (PSYCHS P7, and P8)	0.943	0.881 - 0.976
P4 Perceptual Abnormalities (PSYCHS, P9 – P14)	0.958	0.911- 0.981
P5 Disorganized Communication (PSYCHS P15)	0.856	0.713- 0.935

Median ICC for IRR SOPS pos 0.88, 21 samples, Woods 2019

PSYCHS Qualification Grants

FDA U01 FD008131, FDA U01 FD008650

AMP SCZ Grants

NIMH U01 MH124629, NIMH U01 MH124631, NIMH U24 MH124639

NIMH U24 MH137171, NIMH U01 MH137298

THANK YOU