Qualification Plan for the PSYCHS as a COA for Attenuated Positive Symptoms in Patients at Clinical High Risk for Psychosis

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Methodological Issue Being Addressed

Drug development for early psychosis intervention depends on identifying patients at Clinical High-Risk for Psychosis and assessing illness severity over time.

Commonly-used Clinician-Reported Outcome (ClinRO) developed for schizophrenia, such as the Brief Psychiatric Rating Scale (BPRS) and the Positive And Negative Syndrome Scale (PANSS), measure positive psychotic symptoms, but these instruments were developed before the rise of the clinical high-risk syndrome for psychosis (CHR) concept and do not clearly distinguish between frankly psychotic and attenuated positive symptoms. Only two commonly-used semi-structured interviews have been developed to measure the severity of attenuated positive symptoms over time: the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS). The SIPS defines five attenuated positive symptoms and the CAARMS four.

The U.S. National Institute of Mental Health (NIMH) spearheaded an effort to harmonize them, resulting in the Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS). The PSYCHS assesses 15 attenuated positive symptoms. The current work outlines a proposed FDA Qualification Plan (QP) for the PSYCHS as a Clinician-Reported Outcome. The FDA has accepted a Letter of Intent (DDT-COA-000163) and provided funding (U01FD008131) to support this development.

Introduction

The CHR is a psychiatric syndrome identified in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5), primarily affecting youth and young adults who exhibit multiple, distressing psychiatric symptoms, including delusions and hallucinations which, although not of the severity of full-blown psychosis, are nevertheless experienced as distressing and impairing of daily activities. The condition is listed in DSM-5 as Attenuated Psychosis Syndrome under the construct of "Conditions for Further Study" and as one of four specified "Other Specified Schizophrenia Spectrum and Other Psychotic Disorders." Meta-analytic estimates of point prevalence are 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), making CHR a common, albeit under-recognized, condition.

Attenuated positive symptoms (APS) are defining characteristics of CHR and its severity. "The Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS" (PSYCHS) (Woods, et al., 2024, doi: 10.1111/eip.13457 and available at ampscz.org, Addington, et al., 2024), created by merging two established instruments, is now being used in the AMP® SCZ observational study designed to prepare for future clinical trials supporting drug registration. Such trials would benefit from a Food and Drug Administration (FDA)-qualified COA to evaluate severity of APS symptoms. To potentially address this need, FDA has accepted a Letter of Intent (DDT-COA-000163, https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=182) and funding (U01FD008131) to develop a qualification plan (QP) for the PSYCHS.

We report preliminary results to support methodological decisions for the PSYCHS QP. The targeted population is CHR, a psychiatric condition in DSM-5 affecting youth and young adults (1.7% in the general youth population) who experience distressing attenuated psychotic symptoms that impair daily functioning but are not full-blown psychosis. The PSYCHS is used in the Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) observational study to prepare for future clinical trials supporting drug registration.

Methods

The COA Qualification Plan includes the following:

- 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

We are presenting preliminary data from CHR individuals, aged 12–35, baseline (BL, n = 381) to 3 months follow-up (3M, n=231) completers from the AMP SCZ observational study was used to explore:

- Item level performance: PSYCHS item distribution
- Discriminant and convergent validity: item level and totals PSYCHS scores correlated with BPRS, NSI-PR, OASIS, CDSS, GFS.
- Recall bias
- Clinically meaningful change: Estimation of a cut-off performed with anchor-based methods using the Patient Global Impression of Severity (PGIS) and the Brief Psychiatric Rating Scale (BPRS).
- Criterion validity studies: compare the PSYCHS against the CAARMS and the SIPS.

To collect evidence to support its content validity, we will involve experts in the field and patients with experience with the tool. This will help us ensure that the current inquiries included in the PSYCHS are adequate to elicit the information that assessors need to make appropriate clinical judgments. Through this process, we will review and analyze the tool's content to ensure it is comprehensive, relevant, and representative of the intended construct.

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Disclosure

FDA has accepted a Letter of Intent (DDT-COA-000163, https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=182) and funding (U01FD008131) to develop a qualification plan (QP) for the PSYCHS.

The authors report no conflicts of interest for this work

Conceptual Framework

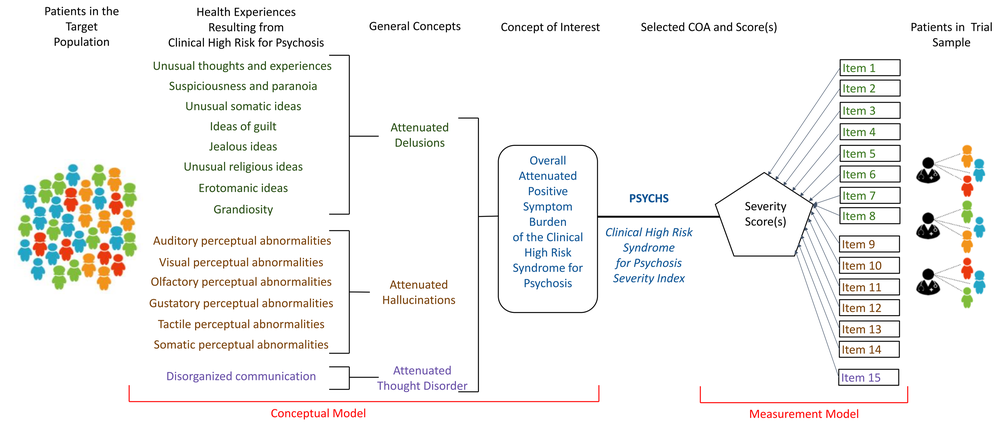


Figure. 1. Conceptual Framework. In the conceptual model, included in the model were selected through a harmonization process of the SIPS and CAARMS, as well as a literature review of the Clinical High Risk Syndrome for Psychosis (CHR). These experiences were harmonized in 15 items or symptoms, each of which can be captured through the use of two or more verbatim inquiries and semi-structured follow-up questions, allowing the assessor to score the severity of the experience. The 15 symptoms were organized into three general concepts: 1) attenuated delusions, 2) attenuated hallucinations, and 3) attenuated thought disorder.

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				
		10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Mild	14 (28.5)	0.4	-2.5	-6.5	-8	-12.2
Moderate	28 (57.1)	1	-2.5	-5.0	-9	-11.5
Severe	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				
		10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Tertile 1 (34-38)	8 (33.3)	-13.30	-10.0	-6.0	-2.25	0.3
Tertile 2 (39-41)	9 (37.5)	-14.2	-10.0	-5.0	-4.0	-0.4
Tertile 3 (43-51)	7 (29.2)	-10.4	-6.5	-4.0	2.0	6.4

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

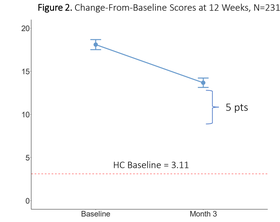


Table 3. Descriptives Total PSYCHS severity scores at Baseline and 12 weeks follow up.

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

PSYCHS Items Performance

Auditory/Visual perceptual abnormalities, suspiciousness, and Unusual thoughts, were the most common symptoms reported in AMP SCZ. Erotomaniac ideas, gustatory, and somatic perceptual abnormalities were infrequent.

Table 4. Frequency of Symptoms with Severity Scores of 3 or Higher

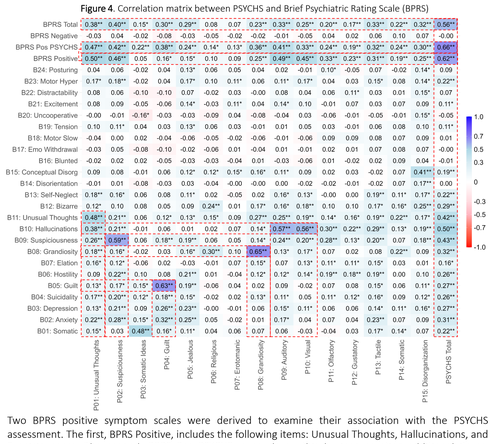
PSYCHS Item	Frequency > 3	%	Mean	SD	Median	Min	Max
P01: Unusual Thoughts	252	66.14	2.81	1.46	3	0	6
P02: Suspiciousness	205	53.81	2.37	1.54	3	0	6
P09: Auditory	182	47.77	2.08	1.77	2	0	6
P10: Visual	161	42.26	1.81	1.62	2	0	5
P04: Guilt	125	32.81	1.77	1.46	2	0	5
P13: Tactile	100	26.25	1.18	1.64	0	0	6
P03: Somatic Ideas	88	23.10	1.26	1.44	1	0	5
P15: Disorganization	77	20.21	1.62	1.17	2	0	5
P08: Grandiosity	44	11.55	0.67	1.22	0	0	5
P14: Somatic	39	10.24	0.54	1.13	0	0	5
P11: Olfactory	38	9.97	0.59	1.25	0	0	5
P12: Gustatory	33	8.66	0.44	1.09	0	0	5
P05: Jealous	27	7.09	0.68	1.08	0	0	5
P06: Religious	26	6.82	0.44	1.01	0	0	6
P07: Erotomanic	5	1.31	0.13	0.51	0	0	4

Figure 3. Severity Scores Distribution for each Attenuated positive symptom at Baseline

Convergent Validity

PSYCH BPRS Item Correlations. There are numerous significant correlations between PSYCHS and BPRS items (Fig. 4). These correlations indicate convergent validity. For example, P1 was found to be associated with BPRS unusual thoughts and hallucinations. P2 was mainly associated with BPRS suspiciousness, while P3 was associated with BPRS somatic ideas, P4 with BPRS guilt, and P5 with BPRS anxiety. P6, P7 and P8 were mainly associated with BPRS grandiosity, while P9 and P10 were associated with BPRS hallucinations. P11 to P14 were associated with BPRS hallucination and suspiciousness. Finally, P15 was found to be associated with BPRS conceptual disorganization.

Figure 4. Correlation matrix between PSYCHS and Brief Psychiatric Rating Scale (BPRS)



Two BPRS positive symptom scales were derived to examine their association with the PSYCHS assessment. The first, BPRS Positive, includes the following items: Unusual Thoughts, Hallucinations, and Suspiciousness. The second, BPRS Pos PSYCHS, expands on this by incorporating additional items: Unusual Thoughts, Hallucinations, Suspiciousness, Guilt, Somatic Concerns, Conceptual Disorganization, and Grandiosity.

Recall Period

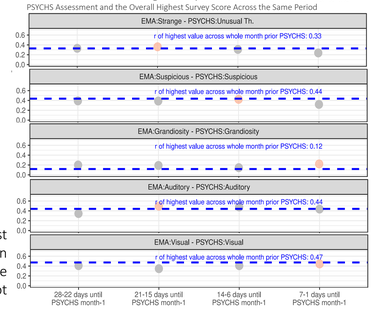
The PSYCHS severity ratings use a "past month" recall period, similar to SIPS and CAARMS, which have also been used with a "since the previous visit" recall in clinical trials. PSYCHS specifically captures the highest severity experienced during this period. Concerns about recall accuracy over longer intervals, such as those raised by Broderick et al. (2010) on pain recall, prompted us to assess the accuracy of monthly PSYCHS ratings by comparing them to daily cell phone survey data on similar symptoms.

Figure 9. Survey Completion Frequency in 7-Day Intervals During the Month Before PSYCHS Assessment

Table 5. Example EMA cell phone survey items and corresponding PSYCHS items

Item	
I felt cheerful	
I felt stressed	
I felt strange	P01: Unusual Thoughts
I felt down	
I felt suspicious of others	P02: Suspiciousness
I felt content	
I felt relaxed	
I felt very special	P08: Grandiosity
I heard things that others could not hear	P09: Auditory
I felt empty	
I saw things that others could not see	P10: Visual
I experienced a negative or unpleasant event	
I experienced a positive or pleasant event	

Table 6. Correlation Between the Highest Survey Scores in Each of the 4 Weeks Prior to the PSYCHS Assessment and the Overall Highest Survey Score Across the Same Period



The monthly PSYCHS rating correlates similarly with the highest survey rating over the past month as compared to its correlation with the highest survey ratings from the past 7 days and each of the past 3 weeks. This suggests that monthly PSYCHS ratings are not biased toward more recent experiences within the recall period.

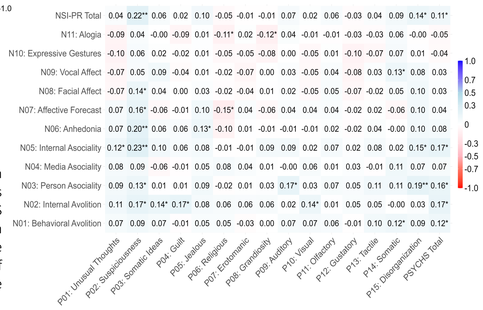
Discriminant Validity

Figure 7. Correlation matrix between PSYCHS Calgary Depression Scale for Schizophrenia (CDSS), Overall Anxiety Severity and Impairment Scale (OASIS)

PSYCH CDSS and OASIS Correlations. The moderate correlation coefficients between total PSYCHS, CDSS, and OASIS scores suggest that attenuated positive symptoms measured by PSYCHS are relatively distinct from depression and anxiety. Guilt items in the PSYCHS scale and CDSS shows medium size positive correlation, indicating some overlap between the experience of guilt in the context of depression and attenuated positive symptoms.

PSYCH NSI-PR Correlations. Only weak correlations were observed between the NSI-PR (negative symptom) items and PSYCHS severity scores suggesting divergent validity. However, P1 (Unusual Thoughts), P2 (Suspiciousness), and P15 (Disorganization) were associated with items related to avolition, anhedonia, and sociability. Specifically, Internal Avolition (N02) and Anhedonia (N06) showed moderate correlations with these psychotic symptoms, with N02 correlating with P1 (r = 0.17) and P15 (r = 0.17), and N06 correlating with P1 (r = 0.20). PSYCHS items displayed only minimal and infrequent correlations with other NSI-PR items.

Figure 8. Correlation matrix between PSYCHS and Negative Symptom Inventory-Psychosis Risk (NSI-PR)



Criterion Validity Study

Two studies are currently underway to validate PSYCHS against SIPS and CAARMS according to the design in Figure 9. An a priori power calculation estimated a sample size of 100 for each study to achieve 95% confidence in obtaining agreement between two raters, with a lower bound kappa of 0.60 (moderate) and a target kappa of 0.79 (very good). The same sample size will be required to compare symptom ratings against the gold standard assessments. This sample is also sufficient to achieve 95% confidence (two-tailed) in detecting at least moderate inter-rater agreement (ICC = 0.74) with 80% power. Based on the 95% confidence interval of ICC estimates, reliability values are classified as poor (<0.5), moderate (0.5–0.75), good (0.75–0.9), and excellent (>0.90)(Koo & Li, 2016).

Table 8. Interim Sample

Group	Female	Male	Total
CHR	16	5	21
Psychosis	3	3	6
Neither	4	1	5
Total	23	9	32

Figure. 9. Study Desing

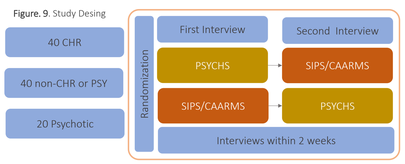


Table 9. Item level agreement SIPS and PSYCHS

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

The results indicate high inter-rater reliability across all PSYCHS symptom domains, with ICC values exceeding 0.85, suggesting strong to excellent agreement. Perceptual Abnormalities (P4) demonstrated the highest reliability (ICC = 0.958), while Disorganized Communication (P5) had the lowest (ICC = 0.856), though still within the good-excellent range. The relatively narrow confidence intervals further support the stability of these reliability estimates.