Study Title: Improving Accessibility and Personalization of Cognitive Remediation for Schizophrenia

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Study Protocol

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Protocol Information:

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Background, Significance and Rationale: Schizophrenia is associated with persistent neurocognitive deficits that do not respond to pharmacologic treatment and add to illness burden by imposing significant limitations on the ability to adhere to pharmacotherapy, benefit from psychosocial programs, and function in the social, vocational, and educational venues integral to community integration. Neurocognition is a crucial intervention target. Cognitive remediation (CR) is an evidence-based practice to treat the pervasive and significant cognitive deficits that contribute to functional decline in schizophrenia. New York State Office of Mental Health (NYS OMH) is the first and largest state system of care to implement a statewide program of cognitive remediation (CR), an evidence-based practice for improving cognition and aiding functional recovery. Through Cognitive Remediation to Promote Recovery (CR2PR), CR is offered in outpatient programs, with plans to expand to more services and further adapt implementation to improve treatment outcomes. This project will work directly with NYS OMH clinics that offer CR2PR to build upon and improve current methods of delivering cognitive remediation.

Purpose: This project studies the impact of two adaptations. One adaptation focuses on increasing the accessibility of the program, which participants report is limited by the requirement of twice-weekly attendance. This project will compare the delivery of CR in either two clinic-based sessions (Clinic) or one clinic and one remote session (Hybrid) per week. The second adaptation is intended to improve personalization of CR by systematically accounting for individual differences in neurocognitive needs. Drawing upon convergent evidence for tailoring CR based on need for early auditory processing (EAP) training, this project integrates a measure of EAP into the baseline assessment to facilitate personalization of the menu of restorative computer-based exercises used in CR. The primary purpose of data analyses is to inform the feasibility and acceptability of the adaptations. The primary outcome will be treatment satisfaction. The secondary outcomes will be change in neurocognition from pre- to post-treatment.

Study Locations: New York State Psychiatric Institute and NYS OMH Facilities:

- ✓ Washington Heights Community Service
- ✓ Creedmoor Psychiatric Center
- ✓ Kingsboro Psychiatric Center
- ✓ Manhattan Psychiatric Center
- ✓ Rockland Psychiatric Center
- ✓ South Beach Psychiatric Center

Description of Subject Population: The study sample includes adults with schizophrenia or schizoaffective disorder who are referred to and eligible for CR2PR.

Procedures: There are two phases of this study.

Phase 1: Staff training and Start up (Months 1-3).

The focus in this initial phase is staff training, using the same combination of web, telephonic and in person training currently in place for CR2PR. Clinic staff trained on cognitive assessment will be provided with and trained to administer the Tone Matching Test as an additional component of the baseline assessment administered for routine CR treatment planning. The CR2PR clinicians will be trained on hybrid delivery methods and to use the Tone Matching Test results to personalize the menu of cognitive exercises such that the treatment plan for only those identified as EAP impaired will include the EAP exercises that are available in the web-based programs used by CR2PR clinics. CR2PR clinicians will be trained on the protocol for Hybrid CR delivery.

Phase 2: Pilot Feasibility Trial (Months 4-36).

The focus of this phase is to implement and evaluate cognitive remediation.

Recruitment Methods: Participants will be recruited from New York State Office of Mental Health (OMH) psychiatric facilities where cognitive remediation (CR) is currently a clinical service (Cognitive Remediation to Promote Recovery, i.e. CR2PR) under the supervision of PI Medalia. Research referrals will be tied to the current system of referrals for participation in each clinic's CR program. Clinical staff will refer potential participants to the CR clinician who will explain the program and invite participation. If clients are interested in CR services, the CR2PR clinician will send all referrals to a research assistant who will explain research procedures, obtain informed consent, and screen for eligibility. Patients who want CR but who do not want to participate in the study will continue with the standard CR service procedures. The research study will not be advertised.

Informed Consent: All clients who agree to an initial meeting with research assistant will have the full study explained to them, and will have ample opportunity to ask questions prior to signing consent. The process of informed consent will include explanation of the amount of time required, the possible risks/benefits of study participation, their right to refuse participation in the study without prejudice and alternatives to study participation, their right to terminate participation at any moment without prejudice, procedures to protect confidentiality, potential for de-identified data sharing, and the contact information for the PI and IRB.

Eligibility:

Inclusion Criteria	**Methods of Ascertainment**
1. Attending OMH Clinic	Referral by clinic personnel to the clinic's CR2PR program
2. Diagnosis of Schizophrenia or Schizoaffective disorder	Medical chart review and/or report from referring clinician and treating psychiatrist
3. Age 18-65	Client report, collected by research assistant
4. Full Scale IQ 70 or above	Wechsler Test of Adult Reading, administered by research assistant
5. English fluency	Wechsler Test of Adult Reading and observation during consent

5. Psychiatric and Behavioral stability	Columbia-Suicide Severity Rating Scale administered by research assistant and clinical team observation

Exclusion Criteria	**Methods of Ascertainment**
1. Unremitted substance dependence / dependence in the past 6 months	Medical chart review and/or report from referring clinician and treating psychiatrist
2. Neurological illness	Client report; Medical chart review
3. Traumatic brain injury in the last 2 years	Client report; Medical chart review

Procedures: A trained research assistant will obtain informed consent, screen for eligibility and obtain additional sociodemographic information. Participants will complete the standard CR2PR neurocognitive assessment battery plus the TMT with a trained clinician. Following completion of the baseline assessment, participants will be randomized using a pre-determined randomization sequence made by the research team to either Clinic or Hybrid CR.

Clinic CR*:* This is the evidence-based CR intervention currently in use at the OMH clinics. The Clinic research arm consists of 30 sessions delivered at 2 times per week in a group format of up to 8 participants with rolling admission. Each session consists of 45 minutes of working on 3-4 computerized exercises to improve specific cognitive skills. CR2PR clinicians are trained to select cognitive exercises from a menu of web-based programs to improve the cognitive functions identified as impaired on the assessment, e.g., attention, memory. With the addition of the TMT, they will be able to identify EAP as a focus area. Computer exercises are followed by 15-minute manualized discussion groups which promote generalization of cognitive gains on computer activities to functional gain by encouraging participants to link within-session cognitive activities to daily activities and recovery goals.

Hybrid CR: The Hybrid condition consists of 15 clinic sessions in the above format, and independent work on cognitive exercises for 60 minutes per week for 15 weeks using a laptop, PC or tablet available to them (at home, school, clinic, library). Independent work on designated web-based computer exercises can be done in multiple or in one sitting. Clients will keep logs of their activities and issues related to remote practice. During the in-clinic session, the clinician will review their remote activities, problem-solve any access or activity related issues, provide personalized bridging, encouragement and feedback, and review the exercises to be completed remotely before the next clinic-based session. Clinicians will also maintain logs of their experiences with remote sessions to document issues pertinent to feasibility and effectiveness.

Throughout treatment in both conditions, CR clinicians document service utilization by tracking scheduled sessions, attendance, treatment dropout and completion. PI Medalia will continue to provide supervision of CR clinicians as a part of overseeing the CR2PR program.

Within one week following treatment completion, clients will be assessed for treatment satisfaction and change in neurocognitive functioning by a research assistant. Treatment completion is defined as at least 20 of 30 clinic sessions for the Clinic condition and at least 10 of 15 clinic sessions for the Hybrid condition. A research assistant will conduct a semi-structured debriefing interview with each participant in the Hybrid condition about their experience using remote technology. At Study months 15 and 30, a research assistant will conduct a semi-structured debriefing interview with each CR2PR clinician about remote technology use and how the tone matching test informed the choice of cognitive exercises.

Criteria for Early Discontinuation: Criteria for early discontinuation from the study will follow clinic-based guidelines. A person is discontinued from a service if they are no longer able to attend due to scheduling conflicts (e.g., work/school), hospitalization for medical or substance use treatment, inpatient psychiatric hospitalization, or discharged from the clinic. The CR2PR clinician will use clinical judgment as to the appropriateness of continued participation for each participant, taking into account evidence of clinical worsening, suicidality, or other issues that may arise during participation. Consultation with the PI will be sought through routine supervision prior to discontinuation. No additional criteria will be used for research purposes.

Assessment Measures: Screening measures include the Wechsler Test of Adult Reading (WTAR-5) and Columbia Suicide Severity Rating Scale. The Tone Matching Test is included in the assessment battery to tailor the CR treatment plan. The primary outcome measure will be treatment satisfaction. The secondary outcome will be change in neurocognition from baseline to post-treatment (approximately 15 weeks).

- **The Wechsler Test of Adult Reading (WTAR-5)** will be used to estimate premorbid intellectual functioning and determine eligibility (Full Scale IQ ≥ 70). This assessment takes 3-5 minutes.

- **The Columbia-Suicide Severity Rating Scale** will be used to assess psychiatric stability. Should suicidal ideation or behavior be endorsed, imminent risk will be further evaluated by the assessor and appropriate, immediate action will be taken. This assessment takes 5-10 minutes.

- **The Tone Matching Test (TMT)** consists of pairs of 100-ms tones that are either the same or differ in pitch between 2.5 and 50%, with a 500-ms inter-tone interval. The participant listens to each tone pair and indicates whether the tones were the same or different. A cut-off score of 70% correct classifies EAP as impaired or intact. This test takes approximately 7-10 minutes and will be administered by the designated clinician at each clinic at baseline.

- **Treatment Satisfaction**: Following completion of CR, all clients are asked to complete a questionnaire rating satisfaction with the treatment experience, working alliance with the CR clinician, and perceived benefits from the intervention. Items are rated on a sale of 1 to 6. The outcome measure is an average of all ratings with higher ratings indicating greater satisfaction. This measure takes approximately 2 minutes to complete. Treatment satisfaction will be compared between groups.

- **Neurocognition:** The Brief Assessment of Cognition in Schizophrenia (BACS) is a standardized battery. Selected subtests will assess verbal memory, working memory, speed of processing, and executive function. The tests will take approximately 25 minutes to complete. It is routinely administered by a designated CR2PR clinician at each clinic before treatment. A trained research assistant will administer the battery at post-treatment. The Continuous Performance Test – Identical Pairs (CPT-IP) is a computerized test that assesses attention/vigilance. Participants view numbers flashed on a computer screen and are to respond when the same number appears twice in a row. The test takes 14 minutes to complete. It is routinely administered by the designated CR2PR clinician at each clinic before treatment. A trained research assistant will administer the test at post-treatment. The outcome measure is an average T score from all neurocognitive subtest T scores. Change in neurocognition will be compared between groups.

Research Related Delay to Treatment: Research procedures will not result in a delay to treatment. All clients will have access to the Cognitive Remediation program provided routinely at their clinic.

Clinical Treatment Alternatives: All clients who decline to participate in research will continue the usual process of intake into their clinic's CR program. They may receive cognitive remediation as usual.

Risks/Discomforts/Inconveniences: The main risk is loss of confidentiality. In addition, patients may become mildly uncomfortable or tired during assessments or during cognitive training. However, no adverse reactions to the assessments or interventions have been reported during the two years the clinical service has been in place at the clinics or in preliminary studies. The software used in this study is the same or similar to that used in clinical practice in New York state OMH clinics with high levels of satisfaction. Although there are no anticipated risks as a function of the assessments or intervention, given that the sample involves people with psychotic disorders, it is conceivable that participants may feel burdened by procedures, or may experience psychiatric symptom exacerbation unrelated to the study.

Methods to Minimize Risk:

Confidentiality: The primary risk is loss of confidentiality. Procedures associated with potential loss of confidentiality, and measures to protect confidentiality are listed in the consent form. A HIPAA Authorization form, reviewed at the time of informed consent, lists those entities with whom knowledge of participation and data may be shared. Confidentiality will be preserved by coding all hard copy data sheets, session logs, and electronic files using a unique numerical identifier not linked to personal identifying information (e.g. name, date of birth). Consent forms will contain identifying information but will not be coupled with numerical identification numbers. Study computers used for collecting and storing data will be encrypted. Hard copy data will be maintained in a locked file cabinet and electronic files will be stored on password protected, encrypted computers, in a locked office at NYSPI. Only the research team will have access to electronic data. Public dissemination of the results of this research will contain no identifying information about individual subjects. Data deposited into appropriate repositories for public sharing will be stripped of any personal identifying information to protect confidentiality.

Burden or Fatigue: During assessments, breaks and refreshments may be provided to minimize burden or fatigue and, if feasible, assessment sessions may be divided. OMH clinicians have been trained to attend to signs of burden or fatigue during assessments and intervention. Participants will discuss their treatment experience with the CR clinician on a weekly basis. This will assist clinicians in trouble-shooting challenges (clinical or practical) to participation and minimize perceived burden. In-clinic, breaks during treatment sessions are and will continue to be offered as needed. Patients completing remote sessions may self-pace their completion of exercises and may do them in a location that is convenient and comfortable.

Unanticipated Adverse Events: A trained research assistant will administer the Columbia-Suicide Severity Rating Scale during the screening appointment to assess psychiatric stability. Should suicidal ideation or behavior be endorsed, imminent risk will be further evaluated by the assessor and appropriate, immediate action will be taken, similar to what is outlined for clinical worsening. PI Medalia will coordinate with CI Saperstein to ensure that all research personnel are trained in safety procedures. Supervision of cognitive remediation clinicians with PI Medalia includes monitoring of patients' clinical stability and ability to continue with treatment sessions. Clinical worsening will be reported to PI Medalia by research and clinical personnel and will be

handled as per clinic safety procedures. Clinical worsening is defined as an increase in symptoms (e.g., hallucinations, paranoia) that causes significant distress, poses imminent risk, and/or impairs the ability of the individual to participate in study procedures. The consent form states that if the participant experiences an increase in symptoms or distress, the study personnel should be informed and will assist the participant in getting the help they need. When research personnel encounter clinical worsening during any study-related procedure they will 1) assist the subject in contacting their primary case worker, therapist, or psychiatrist and 2) report the urgent clinical issue to PI Medalia. In the unlikely situation that a subject is deemed to be an imminent risk to self or others (i.e., expresses imminent suicidal or homicidal ideation), the study personnel will physically walk the subject to their primary case worker, therapist, or psychiatrist. Further course of action may include contacting security to escort the participant to the emergency room or to call 911. Any unanticipated adverse event will be reported immediately to PI Medalia by the cognitive remediation clinician or research personnel.

Certificate of Confidentiality: This study will be conducted under a Certificate of Confidentiality.

Direct Benefits to Subjects: Cognitive remediation and computerized learning software have been used in many psychiatric patient populations in various settings and are well-recognized procedures without serious risk. There is potential for direct benefit to the patient participants, such as improvement in cognition, and potential benefits for the treatment of other people with neuropsychiatric disorder.

Compensation or Reimbursement: Participants will be compensated $40 for the baseline assessment and $60 for the post-treatment assessment.

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