Comprehensive Treatment of Early Course Schizophrenia: A Nonrandomized Study of Long Acting Injectable Antipsychotic Medication Combined with Cognitive and Functional Skills Training

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Rationale.
First episode patients with schizophrenia are very likely to respond well to antipsychotic medications at their first treatment[1]. However, attaining clinical remission does not guarantee either functional recovery or sustained remission[2]. The failure to sustain remission is nearly always due to failures to maintain adherence to treatment[3]. Failure to achieve functional recovery is due to the fact that sustained remission is only one of several factors that are required to achieve recovery, including skills training and other elements of support[4]. Functional recovery rates at the time of the first episode of schizophrenia are below 20% when standard pharmacological treatments are relied as the primary intervention.

There are potential solutions to the shortcomings of prior treatment for first episode schizophrenia. For instance, the use of long-acting injectable medications has been shown to have substantial benefits for early-course patients, similar to their substantial benefits for more chronic patients[5]. Several studies have shown notable evidence of sustained clinical remission and improvement of both brain structure[6] and cognitive functioning[7] in first episode schizophrenia patients receiving these treatments. Accessibility and patient (and family) acceptance of the treatments are current barriers to greater use of these medications in first episode schizophrenia. However, in some studies, acceptance of LAI was as high as 70%[8].

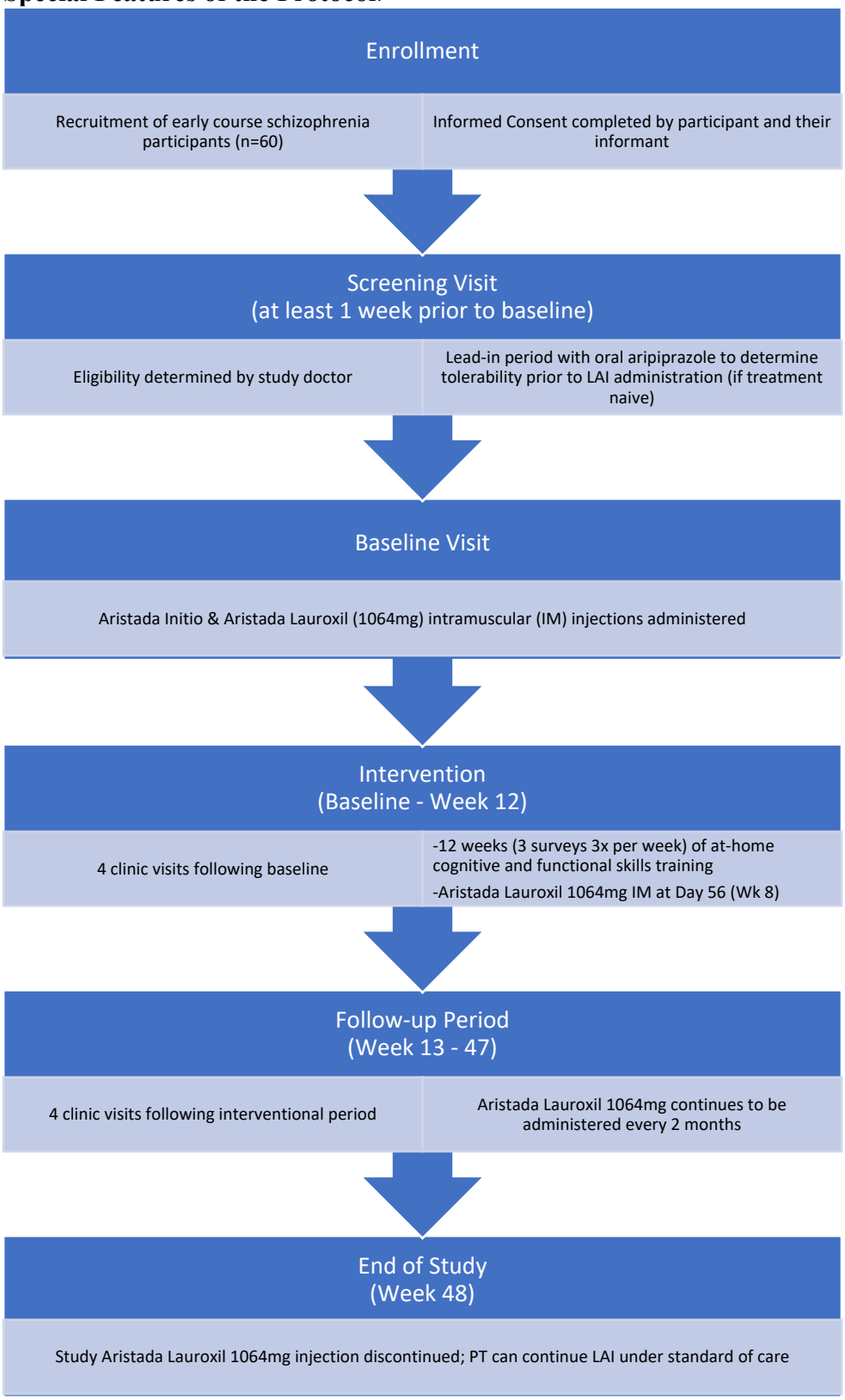
As far as solutions to enhance recovery, combined treatments with psychosocial interventions and computerized cognitive training, referred to as cognitive remediation, have led to substantial gains in chromic patients[9-10] with even greater gains in early-course patients[11]. In a recent study of first episode patients[12], combined LAI treatment, cognitive remediation, and skills training led to substantially higher rates of return to work and school than interventions that did not contain all three of the components. These gains have actually translated into improved social outcomes. As the participants in the Ventura et al. study were all receiving background psychosocial interventions, this suggests again that a combined therapy may be the best approach.

More than with LAI interventions, combined psychosocial and cognitive remediation interventions have had limited access. One possible reason is cost, in that in-person delivered skills training requires a trained professional and may not be covered by insurance. While computerized cognitive training is now available and inexpensive, skills training interventions have lagged behind, possibly because they need to be focused on specific skills, rather than on the global target of cognitive performance. In this study, we will use a newly developed[13] and recently validated[14] computerized functional skills assessment and training program to deliver skills training in concert with computerized cognitive training.

Specific Issues impacting Efficacy of Computerized Cognitive training.
Although meta-analyses have suggested that computerized cognitive training has efficacy in wide-ranging samples of people with schizophrenia[15], there have been some negative studies. One of the common themes of the failed studies is that of poor engagement on the part of some trainees[16]. As we reported, participants with early course schizophrenia, bipolar disorder, and major depression manifested training gains that were correlated with the average of training gains per training day, with number of

days trained not correlated with gains[17]. Further, in a study of people with MCI trained with the skills training software, the average gain in time to completion **per training session** ranged 0.8% to 9%, with a median score of 5%.[18] Thus, we will monitor both cognitive and skills training in real time to identify participants who are not exerting adequate effort.

Special Features of the Protocol.



In this study we intend to offer an enhanced intervention compared to treatment as usual and to offer it to all patients who are being discharged from the hospital who meet inclusion criteria as described below. In this intervention, we will offer Aristada Initio® combined with Aristada Lauroxil ® 2-month (1064 mg) at the time of discharge to early course patients. We will also offer a bundled cognitive and functional skills training program. Patients who are discharged from the inpatient services can receive computerized cognitive training through our clinical services. However, the computerized functional skills training software is not currently delivered at JHS and there is presently no systematized process by which newly discharged patients are referred for the training-based interventions, probably because clinicians are uncertain about the benefits.

As a result, participants who are eligible and agree to participate will receive long-acting injectable treatment and will be followed for at least one year with clinical and functional assessments. The skills and cognitive training program will be offered for 12 weeks, which is a standard course of cognitive remediation treatment. We will index improvement in cognition and functional skills with a structured cognitive and functional assessment at entry to the study, after the 12 weeks of training, and at the end of the one-year period. Functional assessments will be used to index functional recovery. Clinical assessments using the PANSS will be used to examine symptomatic remission and emergency room visits, changes in levels of care, and other milestones will be used to index general clinical stability.

It is difficult to index the extent to which participants will choose to enter the enhanced care research study. Studies cited above have suggested as many as 70% of similar participants chose the LAI option when offered. Given the base-rates of acceptance of other service offers following discharge from JHS, we are anticipating an approximately 30% acceptance rate per admission. As a we will use a rolling entry design, such that participants who decline to participate are recruited at their next admission. Work to date shows our expected patient flow. As noted in specific aims, we anticipate that the earlier a participant accepts participation, the better their outcome will be in terms of remission, recovery, and cognitive and functional capacity performance.

Methods.
Study Design:

Primary Purpose	• Comprehensive treatment of early course schizophrenia using long acting injectibles with computerized cognitive and functional skills training.
Interventional Study Model	• Single group, offered to all patients discharged from the hospital who meet the criteria for the study.
Masking	• We will not be masking in this study since the medication and computerized cognitive and functional skills training will be administered to all participants.
Allocation	• Nonrandomized
Enrollment	• Total enrollment of 60, with anticipation that 40 of these early-course patients with schizophrenia will meaningfully participate in the program.

Overview. We plan on a sample of 40 early-course patients with schizophrenia who will complete the pharmacological and training interventions. We anticipate that we will need to recruit 60 participants to identify this sample of 40 who meaningfully participate in program. This sample size is selected it is practical to recruit, assess, and follow this sample. They will be recruited at discharge from an acute admission or from outpatients who have experienced a relapse after successful treatment. First, eligible subjects will undergo a lead-in period with oral aripiprazole (if treatment naïve) for at least 7 days. The participant will be provided/prescribed the complimentary generic oral aripiprazole by one of our study psychiatrists. They will be assessed at baseline, with clinical, cognitive, and functional assessments, after which they will be treated with the long-acting injectable version of aripiprazole also known by its brand name Aristada Initio and Aristada Lauroxil. They will receive an initial treatment with an injection of Aristada Initio (675mg) and Aristada Lauroxil 2-month formulation (1064 mg). They will receive cognitive and functional skills training for a three-month period and will be followed up for 12 months, while receiving injections of Aristada Lauroxil 1064mg every 8 weeks. Primary outcomes will be sustained clinical remission and evidence of progress toward functional recovery, with secondary outcomes being performance-based assessments of cognition and functional capacity.

Participants: Male and female inpatients with a DSM-V diagnosis of schizophrenia will be recruited. They will have been discharged from inpatient admissions three or fewer times prior to the current episode, unless their total duration of illness is less than 2 years, in which case they will be considered eligible. We will prioritize recruitment of patients who have informants available and willing to participate. We anticipate that we will be able to retain 40 patients to completion if we recruit 60 participants. Patients will be contacted to complete an eligibility screener over the phone per the phone

screening script. Only patients who have expressed interest in participating in the study will be contacted to complete an eligibility screener.

We will be including the use of MyUHealthChart as a recruitment tool to the study. This tool will allow study team members to send recruitment messages to UHealth patients who agreed to be contacted if there are studies where they meet the initial study eligibility criteria. Including the UMiamiHealthResearch.org (the URL): https://umiamihealthresearch.org/studies/20211098 Please review the following documents for further information on this procedure: 1) C-Cog_UMHR_InfoPage & 2) C-Cog_UMHR_InclExcl.

Diagnostic Assessment. We will use the Mini International Neuropsychiatric inventory (MINI[19]) to confirm the diagnosis.

Clinical Assessments. We will use the Positive and Negative Syndrome Scale (PANSS [20]) to assess clinical symptoms of schizophrenia. We will use the Columbia Suicide Severity Rating Scale (CSSRS[21]) to examine suicidal ideation and behavior.

Cognitive Assessment. We will use the Brief Assessment of Cognition-iPad app version (iPad BAC[22]). This fully automated app will be administered at baseline, end of the training protocol, and at the one-year follow-up. There are six tests in the i-Pad BAC and they are automatically scored and recorded. Dependent variable will be the composite score. There are six different forms of the BAC and we will use three different versions for this study.

Functional Capacity Assessment. We will employ the Virtual reality Functional Capacity Assessment Tool, iPad version (VRFCAT[23]). The VRFCAT measures four different functional abilities: checking for the availability of items to complete a recipe, taking a bus, shopping in a store, and managing currency. There are 12 different objectives and for each objective the dependent variable is time to completion. There are six different forms of the VRFCAT and we will use three different versions for this study.

Functional Assessment. There are multiple possible functional rating scales, but many are not suitable for early course assessments. We will use the SOFAS[24]. The SOFAS was the scale used in the Singapore high risk study. It performed remarkably in the study, identifying baseline differences between controls and high-risk cases. Further, it also was sensitive to both decline in the converters and improvements in the remitters. It also showed convergence in course with cognitive performance. it meets all of the criteria that a scale should have. It requires someone who knows the participants well enough to generate ratings, but self-reports are dubious in any case.

Study Endpoint

Primary Outcome Measure: Functional Remission of General Schizophrenia Score	Exploratory Outcome Measure: Functional Recovery of General Schizophrenia
• Description: The Positive and Negative Syndrome Scale (PANSS) is a # item scale where a score of 3 or less would indicate remission • Measure Timeframe: 6 month follow-up	• Description: Participants continuing to make progress and achieve success across functional domains, measured by the informant's SOFAS assessment, in comparison to available data • Measure Timeframe: 12 month follow- up

Definition of Remission. We will use the widely adopted Andreasen et al. criteria for remission. The clinical information will come from the PANSS[25]. In order to meet criteria for remission, subjects had to have scores of 3 (Mild) or less on all of the critical PANSS (Delusions (P1), Hallucinations (P3), Unusual Thought Content (G9), Conceptual Disorganization (P2), Mannerisms and Posturing (G5), Blunted Affect (N1), Social Withdrawal (N4), and Lack of Spontaneity (N6). This determination will initially be made at the 6-month follow-up of the patients, thus requiring that patients be in remission 6 months after initiating treatment with Aristada Lauroxil regimen.

Definition of Recovery. By its definition, recovery is a long-term concept and not suitably addressed in a one-year study. We will define progress toward remission based on our previously published criteria for functional remission[26]. We will identify the proportion of cases who are making progress and achieving success across functional domains. Information for these determinations will come from the SOFAS assessments conducted with their informants. The SOFAS is well suited for collection of these data because the assessment is structured to examine these three central domains of everyday functioning. As noted above, the SOFAs has shown excellent sensitivity in informant-based interviews in cases whose clinical and functional state was fluctuating.

Interventions

This is a single group study. All participants will be given the same dose of the LAI (unless study doctor determines it is in the best interest of the patient to have the dose reduced, unrelated to an independent study arm) and will be administered both of the following computerized cognitive and functional interventions:

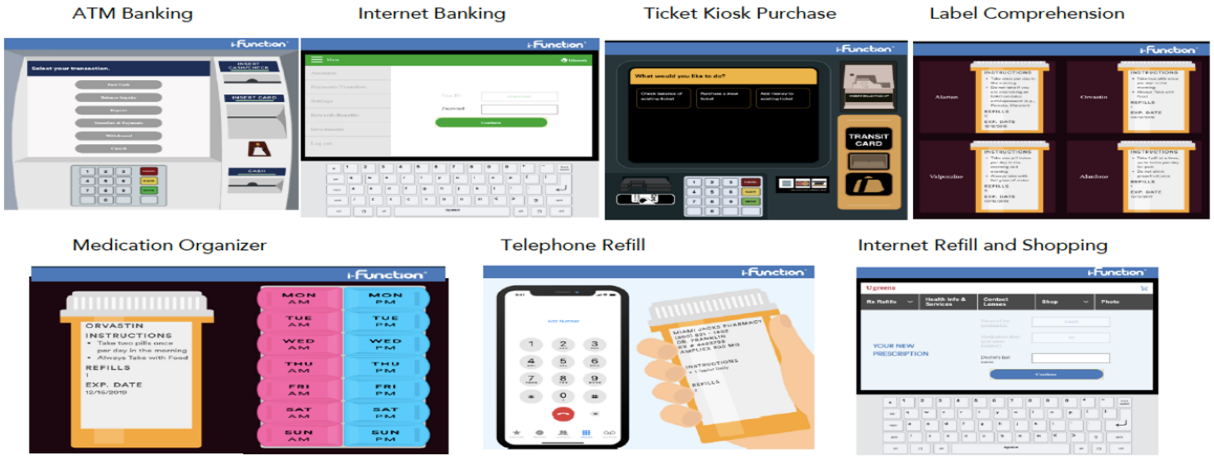
Computerized Cognitive Training. The CCT training will consist of the Posit Science Brain HQ CCT Double Decision. Double Decision was the training protocol in the ACTIVE study[27] that was associated with major and persistent cognitive gains after 14 hours of training in healthy older people. We choose this CCT package as it is evidence-based, easily deliverable without customization, and accessible to schizophrenia participants as evidenced by our prior studies. The initial training will take place at the data collection site (i.e., Brain Fitness Center at UM) until the participant demonstrates an ability to use

the program independently. Once it is established that they can launch the program and proceed through the modules, training will occur in the participants' home setting.

Functional Skills Assessment and Training (FUNSAT). This training system was developed at UM and contain six different modules: ATM and Internet Banking, Telephone and Internet prescription Refill, Ticket Kiosk Purchase, and Medication Management. FUNSAT is being delivered on a tablet device or a full-size laptop or desktop computer. The FUNSAT training consists of six separate training modules, which include subtasks increasing in difficulty, covering 4 different functional skill domains. Training occurs over 12 weeks with a recommended dose of two, one-hour sessions per week, which are split between 30 minutes of skills training and 30 minutes of Brain HQ.

Study Assessments and Procedures

Figure 4 Training Tasks and Visual Depictions



Participants will train on two FUNSAT tasks per day, with the order of training determined by the program. The training component will: 1) Identify the current levels of an individual's ability on the functional task of interest with Item response theory (IRT)-based strategies and start training there; 2) Use dynamic-titration feedback from immediately proximal task performance to adjust the difficulty of task demands to optimize training potential; and 3) Provide immediate trial by trial feedback and, most critically, instructional responses following errors, followed by repetition of the previously failed item. Training occurs on the FUNSAT until they "graduate" from the program or 12 weeks has elapsed. We are defining "graduation" on a task as the completion of all of the modules of the task two times in a row with **no more than one error per module**. This definition captures task completion without any instructions, because a single error in the training conditions leads only to repetition of the instructions. Thus, "graduation" from the program as a whole means that the participant has completed all tasks twice in a row with no more than one error per module. After graduation participants will continue to train for their full complement of 24 sessions on Brain HQ.

Measurement of Training Engagement. As noted above failure to engage in training leads to poor gains. Both of our training software programs allow for remote monitoring or training engagement, through cloud-based portals. We have identified threshold levels for minimal training engagement and will provide feedback to all participants who are training below that level. Subthreshold trainees will be encouraged to make more effort, but we will not eliminate them from the study, in order to be able to relate levels of engagement to training gains, cognitive improvements, and remission and recovery. Study coordinators will send messages to trainees who are not making progress in training.

Pharmacological Treatment Protocol.
For patients who have never taken aripiprazole, the participant—with prescription from our study psychiatrist --will establish tolerability with oral aripiprazole prior to initiating treatment with Aristada ® Initio. Due to the half-life of oral aripiprazole, it may take at least 7 days to assess tolerability (lead-in period). After establishing tolerability with oral aripiprazole, we will administer the first Aristada intramuscular injection (1064 mg) in conjunction with both: One 675 mg injection of Aristada Initio ® in the deltoid or gluteal muscle. We will aim for concurrent administration to minimize non-adherence to the protocol. Subsequent 8-week injections of Aristada Lauroxil ® 1064 mg will be scheduled and will coincide with assessment visits (See schedule of events). We will only adjust the Aristada Lauroxil ® dose based on tolerability, as this dose is required for full 8-week duration of efficacy. This may require the participant to adjust his/her injection frequency to maintain clinical efficacy.

Ecological Momentary Assessment (EMA) surveys
Participants will be asked to complete ecological momentary assessment (EMA) surveys on a smart device, either their own or one provided by the investigators. Surveys will be sent 3 times per day, 3 days per week, during the 12-week cognitive and skills training period. Thus a total of 108 possible surveys will be sent. The window to answer the survey will be 60 minutes, with reminders every 15 minutes. Days where there are no surveys answered will be pushed to the next day and the entire procedure survey will be repeated verbatim, so that at least one survey is answered every day. The time frame for the survey is "Today" for the first survey and "In the last hour" for the next two. Participants are asked about their typical wake-up hour and the first survey is launched one hour or more after this time. The EMA application will be downloaded from the App Store and will not interact in any way with any of the other applications on the participants' phones. Data will be uploaded directly to an Amazon Web Services (AWS) encrypted portal. No personal health information is attached to the surveys.

Surveys begin with a query regarding location (home vs away) and social context (alone vs. with someone). Then a customized activity survey is presented, customized for the combination of location and social context (home alone, home with someone, away). Following the activity survey, 4 mood questions are asked (Happy, Sad, Relaxed, anxious) and rated for intensity. Then four psychosis questions will be asked (Hearing voices, feeling paranoid, getting messages, having special powers), which are answered on a yes/no basis. Surveys take approximately 3 minutes to answer, and participants are compensated $1.00 per survey, payable at their next in-person visit.

Inclusion criteria
Adults (Age 18 years and older)
Fluent and literate in English and able to consent

Diagnosis of schizophrenia (Confirmed by the M.I.N.I. assessment)
Current Hospitalization or outpatient relapse
Fewer than four previous admissions
Willing to accept long-acting injectable treatment and participate in rehabilitation
Willing to undergo a lead-in period of oral aripiprazole (if treatment naïve)
Informant willing to participate
Participant willing and able to provide written informed consent

Exclusion Criteria
Primary diagnosis other than schizophrenia
Prior failed or intolerable LAI treatment
Current Suicide Risk
Hypersensitivity to Aripiprazole
Pregnancy
Positive illicit drug screen other than cannabis (rescreening allowed in 4 weeks for drug positive cases)
Unable to give personal informed consent
History of treatment resistance as evidenced by clozapine treatment
Unable to stop treatment with medications that are strong CYP2D6 or CYP 3A4 inhibitors and or strong CYP3A4 inducers (2.3, 7.1) for at 14 days prior to initiation.
Have any condition that, in the opinion of the investigator, would compromise the well-being of the patient or the study or prevent the patient from meeting or performing study requirements.

Side Effect Assessment. As the occurrence of significant side effects with Aristada Lauroxil has been reported to be low: insomnia (8.4%), increased weight (5.0%), Akathisia in (3.8%), and AEs related to metabolic parameters (4.6%) of patients, we will not perform formal side effects rating scales but rather will inquire at visits about sleep, akathisia, and weight gain using structured queries.

General Methodological Approach. Providers from both UM and Jackson will introduce the research to patients under a physician-patient relationship. If a patient is interested in learning more about the study, the provider will reach out to the study team with the patient's permission (ie. Using a pre-screening authorization form). The designated study team member will approach interested inpatients or outpatients at JMH who we know to possibly meet criteria and explain the study to them and their caregivers/informants. All interested participants will have the procedures explained by designated study staff. Patients who meet criteria and are eligible and interested will sign an informed consent form approved by the University of Miami Institutional Review Board. Initial assessments will be performed by trained study coordinators. Those participants meeting diagnostic criteria will receive PANSS and CSSRS assessments performed by the same coordinators. Assessments of cognition and functional capacity and the SOFAS will be performed by different assessors. Testing of tolerability, if needed, will happen as soon as informed consent is obtained. Injections of Aristada Initio and Aristada Lauroxil will be administered immediately after baseline assessments of cognition, clinical symptoms, and everyday functioning.

Individuals who decline to participate will be approached after any readmissions to JHS and offered the opportunity to join the study at that time. Potential participants will be approached at all future admissions. Further, the "admissions clock" will not advance for these cases after the first time that they are approached for participation, such that a potential participant with three previous admissions when

they are first approached will not be disqualified from participation regardless of the number of additional admissions they experience prior to agreement to participate.

Reassessments will be performed in line with the schedule of events below. There are a total of 11 in person assessments over the one-year study period. After the first 4 weeks of the protocol these assessments are linked to injection events. Training will start at the Brain Fitness Pavilion at UM, in the same building as the inpatient units at JHS, and training will be delivered in person by the staff at the Pavilion. These trained staff members will also determine when they believe that the participants are ready to train at home. When they are ready, the participants will be provided with a tablet device and an account for FUNSAT and Brain HQ, both of which are accessed through the cloud.

In order to avoid recruiting participants who are overly interested in receiving compensation and not interested in training gains, we will not compensate participants for training sessions. Instead, we will compensate participants based on training gains. Further, there are no payments for screening and payments for in-person assessments (visits 3-12) are budgeted at $25.00 each other than baseline, which will be compensated at $50.00 because of its length. Each of the 6 simulations graduated by the participants will lead to a payment of $20.00. As Brain HQ training happens the same time as skills training, we will not be compensating participants for Brain HQ training until after graduation from all 6 skills training modules.

Participants who no longer want to continue training will be continued in the pharmacological protocol if they want to. They will be allowed to resume training at any time in the 12 months after their study entry.

Data Management
We will use UM REDCap to capture the clinical assessment data and retain de-identified variables for this research project. Source documents will be retained in paper format in appropriate study binders. We will keep a scanned copy of source documents in BOX. Data from the BAC-App, VRFCAT, Brain HQ, and Funsat are directly uploaded to the cloud (Microsoft® Azure) and are stored without identifiers.

Statistical Approach.
A sample size of 40 participants is generally consistent with the ability to identify a moderate effect size compared to other treatments. However, we will compare our results to previous outcomes because of the lack of a control group (due to cost). Previous data regarding rates of functional recovery for first episode patients are 15-20%. Thus, if compare our expected rate of recovery, based on the results of the UCLA studies, as 60% compared to 18%, we find that at $p<.05$, $n=40$, power =1.0 for detecting this difference. If we drop our expected recovery rate to 50%, power=.95, and if we drop it to 40%, double the previous rates, power is .90.

In this study we collect both categorical information (Remission, Y/N; Recovery, Y/N) and quantitative data (PANSS scores, Cognitive Performance, Functional capacity performance, and Functional outcomes ratings). There are also several covariates, such number of previous admissions, demographics, and the number of times participation was offered to the participant before they agree to participate.

For the categorical information, we will use Logistic regression models for binary outcomes. For the quantitative variables we will use a Mixed Model Repeated Measures (MMRM) to compare changes in the outcomes variables across visits and to evaluate possible covariate influences.

PANSS total and subscale scores are collected at all visits from 2-12. Cognitive performance, VRFCAT performance, and SOFAS scores are collected at visits 2, 7, and 12.

We will examine the time course of clinical response on the PANSS from visits 2-12 using MMRM. To examine reduced risk of relapse, a Cox proportional Hazards model (i.e., survival analysis) will examine the group who agreed to participate to those who declined participation for time to readmission to the hospital. The dichotomous variable of relapse will be the outcomes measure.

In order to evaluate continued improvement on the BAC app and the VRFCATs across visits, we will again use MMRM, with subject as a random term and treatment engagement as the covariate. These analyses will be run separately for the cognitive and functional capacity outcomes.

In order to evaluate prevalence of functional recovery compared to prior standards, we will compare the proportion of cases who manifest evidence of functional recovery at their final assessment to previous standards. We will compare the observed proportion of recovery and compare it to a very liberal prior criterion of 20% and use a Mantel Hansel test to compare the two proportions.

Protection of Human Subjects. We will use all possible means to ensure protection of human subjects. We will collect signed informed consent from all participants. As we are offering approved medication treatments at approved doses, as well as only performing assessments that are in common clinical use, the risks of this project are no greater than standard clinical treatments. Similarly, both the skills and cognitive training protocols have been designated as no more than minimal risk for participants by the UM IRB in a previous study.

Risks.
The treatments in this study are approved by the US Food and Drug Administration for treatment of schizophrenia at the doses administered. As a result, treatments are in common clinical use and there are no more risks than those associated with standard treatments for the condition. The assessments used are also in common clinical use, as are all of the digital treatments delivered. Thus, the only risks associated with research participation are threats to confidentiality and avoidance of coercion. All assessments and training procedures that use the cloud have met CFAR part 21 compliance for data collection and storage of data. Signed consent documents will be stored in a locked cabinet in an office that is not on the treatment unit nor at the Brain Fitness Center.

We will not use the treating MD or ARNP as the recruiter for the study, so that no one will be recruiting their own patients. Consent will be collected by a study team member who has no clinical connection with the participants. We will obtain a partial HIPPA waiver so that we can identify potential participants from their medical records and be prepared to recruit them when they are readmitted.

Potential participants who decline to participate will be approached with the same recruitment strategies if they are readmitted to JHS. They will also be informed that if they want to enroll after discharge, they can contact the study team and enter the study at any time if they remain qualified for the study.

This trial will be posted on clinicaltrials.gov as soon as the agreement between UM and the sponsor is finalized.

Adverse Events:
Almost all research studies involve some risk. These medication treatments, Aristada Initio® and Aristada Lauroxil®, have already been approved for this condition and the reported occurrence of side effects is low for both:

- Akathisia
- Insomnia
- Weight gain
- Problems with metabolism (increased cholesterol, triglycerides, or hyperglycemia)

Serious Adverse Events:

Important safety information about serious adverse events for Aristada Initio® and Aristada Lauroxil® that would result in hospitalization or serious medical emergencies are less common, but rare instances that have occurred to other patients on these medications are listed below:

- Cerebrovascular problems
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Uncontrollable compulsive urges
- Orthostatic hypotension
- Risk of falls
- Low white blood cell count
- Convulsions
- Problems controlling body temperature
- Difficulty swallowing

Confidentiality.
All information will be kept confidential. All source documents will be kept in a locked cabinet. Only UM-approved applications will be used to store de-identified information electronically such as UM BOX and UM REDCap, other than the Cloud-Based data collection for the digital measures.

We are requesting a partial HIPAA waiver to recruit patients at Jackson and UM. In order to follow up with potential Jackson patients who may qualify, we are requesting access to a secure JHS SharePoint to maintain name and contact information for potential patients. Patients will sign an appropriate authorization for pre-screening for the study.

Choose the statements below that are applicable to this research:

15(a). ☒ Data will be collected from the EMR or subjects at UHealth or JHS. *If checked, answer the following:*

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB. (Complete Section 17 below)

15(b). Data collected:

☐ Will not include Protected Health information or Personally Identifiable Information

☒ Will include Protected Health information or Personally Identifiable Information

15(c). How will the research store the data?

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)
☒ On a cloud-based storage system that is approved by the University of Miami
☒ Other, specify: paper source

Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that **does not include any** indirect or direct identifiers (listed in the instructions for Section 15 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 15 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. **The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.**

15d. Jackson Health System additional requirement

☐ This section is not applicable because the research is not collecting health information from JHS under a waiver of authorization (without obtaining a HIPAA authorization from the participant)

If health information, including Protected Health Information and/or Personally Identifiable Information are collected from JHS without a signed authorization from the subject (with a waiver of authorization from an IRB or Privacy Board), you must agree to the following:

☒ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research with a waiver of the requirement for an authorization under HIPAA shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 15 of this protocol.

If the data obtained for this research will be acquired from a retrospective "chart review" involving health information from JHS with a waiver of authorization (without obtaining an signed HIPAA authorization from the subject) then the data and the link and/or key to each subject's identity shall only be maintained in the secure JHS SharePoint environment made available by JHS.

Provisions to Protect the Privacy Interests of Subjects

All authorized staff will be CITI-trained and will be limited to only 1-2 staff who are on the protocol as the main coordinators. Any staff that will use UChart or Cerner will receive the appropriate trainings and clearance before receiving access.

Waiver of Authorization for Use and Disclosure of Protected Health Information (HIPAA)

☐ This section is not applicable, we are not requesting a waiver of authorization.

We are requesting a partial HIPAA waiver. For Jackson patients, we will ask patients to sign a JHS pre-screening authorization form.

A partial waiver of HIPAA authorization is requested to access medical records, in-person screening, and phone screening of potential participants for the purpose of pre-screening inclusion/exclusion criteria by Dr. Harvey or his backup in addition to study coordinators and research assistants. **Pre-screening**: Potential participants will be given information about the study, asked brief screening questions conforming to the inclusion/exclusion criteria, and asked if they are willing to come in or be visited in the community to learn more about the study and undergo the informed consent process. For preparatory research for the phone screening, we are requesting a partial waiver of documented consent and partial waiver of HIPAA authorization, and requesting to obtain oral consent. PHI collected at

phone screening includes name, phone number to recontact after eligibility is determined, and email address to send directions to their first visit (if eligible). All PHI will be kept locked in the offices of the PIs or their study staff and only PIs and study staff will have access to PHI. This study cannot be conducted without partial waiver of consent and HIPAA authorization as it is necessary to collect PHI and screening questions in order to: determine eligibility, limit subject burden on those that are not eligible, and communicate (e.g., call back with eligibility status) with potential subjects.

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.

☒ ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

If you are collecting health information from JHS under a waiver of authorization, you must read the paragraph below and sign the signature block to indicate your agreement:

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

07/22/22

PI Signature Date

Benefits.
In addition to providing commercially available long-acting injectables and cognitive trainings at no cost, participants would be monitored over the course of one year and actively monitored for suicidal ideations. The generalizable knowledge from evaluating the effect of combined therapy on patients with schizophrenia will help investigators advance future treatments.

Compensation.
Participants will be paid by either cash or debit card or alternative method (e.g. Money order, gift card, Zelle). If by debit card, they will be issued a reloadable debit card that can be used for studies at the University of Miami. The study staff will provide information about how the card works. The card will be loaded according to the payment schedule. The company administering the card requires name,

address and date of birth entered online for payment; mobile phone number and/or email address are optional and only for study related communications. This information will only be used for payment and communication purposes and will not be given to another company or linked to any of the study data.

DSMB

We will establish a DSMB from UM faculty members who have no connection with the protocol and no connection with i-Function. As the trial is not randomized, there is no blind to protect. As the medications are approved for their uses, all adverse events will be reported through the U.S. FDA surveillance system, as well as to the study sponsor.

Resources Available

All study staff involved in subject assessments will be CITI-certified and IRB-approved. Each study team member will complete protocol and scales training with our investigator(s) or with our senior research staff. Our senior staff have 3-5 years of experience in psychiatric protocols and scale administration.

Setting

All consenting and assessment administration will be done in our Psychiatry space at the Jackson Behavioral Health Building. The University of Miami has three rooms that are rented 3302A, B, and D. All procedures will be conducted in our UM space.

Process to Document Consent in Writing

Documentation of the initial consent discussion and any re-consenting discussions must be adequately documented in the subject's records and should include the following:

- The subject's current capacity to give informed consent should be evaluated and documented prior to the consenting discussion. Documentation should include how competency was evaluated.
- Date of the consent discussion.
- Statement confirming that no study-specific procedures were performed prior to obtaining informed consent or assent (if applicable).
- Name of person conducting the consent discussion and the names of the persons involved in the consent discussion, and their relationship to the subject (e.g., subject, LAR, witness).
- Summary of significant questions asked by the subject.
- Statement confirming that the subject were given a copy of the fully-signed informed consent document.

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Schedule of Events and Assessments

	Screening	Baseline			1m	2M	4M	6M			
Visit Day	**-7 (at least)**	**0**	**Day 7**	**Day 14**	**Day 28**	**Day 56**	**Day 112**	**Day 168**	**Day 224**	**Day 280**	**Day 336/ EOS**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit window (days)	**0**	**0**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Type of Visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Medical history and demographics	X										
Psychiatric and neurological history	X										
Physical examination	X										
PANSS	X	X			X	X	X	X	X	X	X
Orthostatic vital signs, weight, and BMI	X	X				X	X	X	X	X	X
Height	X										
Pregnancy test	X	X									
Urine drug screen	X	X									
SOFAS		X					x				X
BAC App		X					x				X
VRFCAT		X					x				X
At-home Cognitive training (Brain HQ, FUNSAT)			2 weekly sessions for 12 weeks								
Inject study drug		X				X	X	X	X	X	
CSSRS	X	X	X	X	X	X	X	X	X	X	X
Side Effect Assessment	X		X	X	X	X	X	X	X	X	X

Note. Weeks 1-12 will include 2x weekly cognitive and functional skills training.
Note. Aristada Initio and Aristada 2-month formulation on BL day

PI or psychiatric resident will collect the psychiatric history and perform the physical examination if no recent examination is available.

Medical History will be collected by the study co-ordinator

Drug screens and pregnancy tests are budgeted into the protocol.

Clinic visits on days 7, 14, and 28 will involve meeting with study the co-ordinator only unless and issue arises with suicidal ideation or behavior.

At each injection visit, the injection will be performed either by the PI, a psychiatric resident under his/her supervision, or the Nurse Practitioner assigned to the participant, who ask about side effects. At each injection visit, we will perform the PANSS and the CSSRS (Study co-ordinator).

All injectable Aristada Initio and Aristada Lauroxil doses are provided by the sponsor.