Project Title: Reducing the Burden of Chronic Psychotic Disorders in Tanzania (CAPACITY)

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Protocol Version Date: January 7, 2019

Overview: Antipsychotic medication is a critical component of treatment for individuals with chronic psychotic disorders (CPDs) in conjunction with psychosocial approaches that support patients and families. Unfortunately, poor medication adherence is common, impedes recovery and increases burden. In Sub-Saharan Africa (SSA), poor adherence is seen in approximately half of individuals with CPD and is a major driver of relapse [6-10]. Care approaches that promote adherence, take advantage of existing resources and which can be readily scaled and implemented in SSA settings, have the potential to greatly advance care and reduce the burden of CPD.

The burden of CPD in Africa: In SSA, brain disorders are the most disabling conditions among people ages 10–44 [11-12]. CPD causes symptoms such as hallucinations, delusions, disorganized communication, poor planning, and reduced motivation. Quality of life is impaired and personal and occupational goal attainment is sub-optimal. Care for CPD includes both psychosocial and pharmacologic interventions (i.e. antipsychotic drugs) along with ongoing monitoring of health status [13]. This may be challenging in resource-limited settings where staff are sparse and/or undertrained. Importantly, forecasts of mental health human resource demands predict continued deficits compounded by increasing disease burden [14].

CPD relapse results in hospitalization, treatment resistance, and cognitive impairment due to progressive structural brain damage [15]. The limited number of CPD relapse studies done in Africa suggest that co-morbid depression, poor medication adherence, and side-effects are the factors most likely to increase relapse [16]. A Tanzanian study found that people with CPD and their caregiver's perceived non adherence to antipsychotic medication as a leading risk factor of relapse [10].

Medication adherence is sub-optimal; use of long-acting injectable antipsychotic (LAI) medication may help maintain adherence: The link between poor adherence and relapse is well known [17-21]. Even gaps in medication treatment as short as 1-10 days can double the risk of relapse [22]. Additionally, poor adherence imposes a large economic burden both on patients' families [23] and society in general [17, 24-25]. Poor adherence risk factors include younger age, poor insight, negative attitude towards medications, shorter duration of illness, poor therapeutic alliance and poor social support [6, 26-29]. In SSA, poor adherence in CPD is a substantial problem. A Nigerian study found non-adherence rates in the order of 35% - 56% [7-9,30].

Because a major obstacle to medication adherence in CPD is difficulty with consistent medication routines [2,31], LAI can be an attractive treatment option for some individuals. LAI can be administered monthly or even less frequently (newer drug formulations can even be given every 3 months), eliminating the daily need to take medications, which in itself can be a stigmatizing behavior [32]. But, medication in itself is unlikely to modify long-term attitudes and behaviors. LAI is not a stand-alone care approach for CPD [5,33].

Health workers in mental health and primary care settings can promote adherence, support patients and families: Nurses and social workers play a key role in monitoring patient progress and facilitating long-term treatment adherence in CPD. A cross-sectional survey of 4120 nurses from Europe, the Middle East and Africa [34] found that nurses perceived 54% of patients to be at least partially non-adherent. Most nurses (90%) reported experience with administration of LAI, with 24% administering >10 injections per month. The majority (85%) of nurses believed that improving adherence would improve patient outcomes. Nearly half (49%) reported that most of their patients depend on a family member caregiver to remind them to take their medication. Most nurses (92%) felt that ensuring continuous LAI would yield long-term benefits for patients.

In spite of the fact that both LAI and health workers who can promote CPD recovery are available in resource-poor settings, there are few widely used care approaches that combine LAI with a complementary psychosocial approach [35]. In SSA, the need for effective adherence promotion approaches is even greater considering the common oral medication "stock-outs," high-levels of stigma

and limited resources to quickly intervene when individuals with CPD skip medication and begin to experience signs of relapse.

In summary, given the extensive burden of CPD in Sub-Saharan Africa, and serious consequences of poor adherence, care approaches that are brief, practical and customized for the care setting have potential to be a game-changer for individuals with CPD. With adherence appropriately addressed, care focus can shift to long-term recovery and social integration.

Purpose:

Overview: The proposed, three phase project will refine and test a first-ever care approach in SSA that combines LAI with a behavioral program specifically intended to promote medication adherence in chronic psychotic disorders (CPDs). In addition to the novel focus, innovative elements include: 1.) a manualized curriculum that targets specific barriers and facilitators to medication adherence in Tanzanians with CPD, 2.) targeting known, high-risk individuals with CPD (those who miss ≥20% of prescribed antipsychotic medication, and 3.) using existing injection clinic health workers to deliver the adherence promotion program. Strengths include the highly generalizable methods and use of LAIs that are available in low-resource settings.

Aim 1: To conduct a mixed-method (quantitative + qualitative) analysis in 100 individuals with CPD to better understand antipsychotic use, adherence barriers and adherence attitudes in Tanzania. Phase 1 methods will include quantitative evaluation of adherence barriers and reasons for non-adherence among individuals with CPD who have been recently hospitalized with relapse related to sub-optimal adherence. The quantitative adherence evaluation will build upon a standardized adherence vulnerabilities screen developed at CWRU for use in homeless people with schizophrenia/schizoaffective disorder. Qualitative assessment (individual interviews with patients, focus groups with families/support persons) will elicit information from stakeholders (persons with CPD, family, support persons) on preferred approaches to deliver adherence promotion interventions

Aim 2: After completion of the Aim 1 assessments, the study team will adapt a successful CPD adherence enhancement approach (Phase 2) based upon findings from Phase 1. Like the original CAE-L program, the intervention will be described in a detailed manual /curriculum that will facilitate future broad-scale dissemination.

Aim 3: In Phase 3/Aim 3, the study team will select appropriate measures, train staff and build capacity in measure implementation, and finalize the intervention for delivery by healthcare workers. Finally, in a training/proof-of-concept exercise, the healthcare workers will implement the adapted CAE-L in a high-risk sample of Tanzanians with CPD (individuals with schizophrenia or schizoaffective disorder who have had recent medication adherence problems). Taken together, the proposed project has substantial public health importance. It will provide the prerequisite materials, training and infrastructure needed for a prospective trial in reducing CPD burden and improving brain health in Tanzania and other countries in Sub-Saharan Africa.

Study Design:

Phase 1

In Phase 1/Aim 1 the investigators will implement a mixed-methods (quantitative + qualitative) adherence assessment battery that will identify salient barriers to treatment adherence in people with CPD. Data collection and procedures will follow those previously successfully used by this team. Qualitative assessment will be conducted using a combination of individual and group-format methodologies. A “deliverable” of Phase 1 will be a summary report that describes barriers and facilitators to treatment for CPD from the perspective of patients, families and care providers.

Quantitative assessment: Drawn from iterative pilot work (32,36 40-41), CAE is flexibly delivered as a series of up to 4 treatment modules whose use is determined based upon an individual’s reasons for non-adherence (adherence barriers) identified at baseline. The modules are Psychoeducation focused on medication and consequences of missing medication, Modified Motivational Enhancement Therapy (MET) to address non-adherence related to substance use, Communication with Providers to facilitate appropriate treatment expectations and optimize management of feared or experienced side effects, and Medication Routines intended to incorporate medication-taking into lifestyle. Prior to delivering CAE,

adherence barriers are evaluated with two standardized measures, the Rating of Medication Influences (ROMI) (42) and the Attitudes toward Mood Stabilizers Questionnaire (AMQ)(43-44). To better understand adherence barriers in the proposed setting, the ROMI and AMQ will be administered to 100 individuals with schizophrenia or schizoaffective disorder who self-report missing 20% or more of antipsychotic medication within the last month, an established benchmark for poor adherence (35). Patients will be ≥ age 18 with schizophrenia or schizoaffective disorder.
Patients will be recruited from Muhimbili National Hospital and its associated ambulatory clinics.
Additional information will include demographic and clinical characteristics relevant to CPD relapse. Adherence assessments will include the Tablets Routines Questionnaire (TRQ) (46-47) and the Drug Attitude Inventory (DAI) (48). CPD symptoms will be assessed with The Brief Psychiatric Rating Scale (BPRS) (50). Global psychopathology will be measured with the Clinical Global Impressions (CGI) (51). Life and Work Functional status will be evaluated using the Social and Occupational Functioning Scale (SOFAS) (52), Substance use will be measured with the Alcohol Use Disorders Identification Test (AUDIT) (53) and Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (54).

Qualitative assessment: The study team will conduct individual interviews of patients with CPD and focus groups with family members and with healthcare workers. The qualitative sample will be derived from Phase 1 quantitative survey participants and target a representative sample with respect to age and gender. Family members will be those of enrolled Phase 1 patients with CPD. Focus groups and interviews will use an adapted semi-structured guide used in NIH-funded trials conducted by Drs. Sajatovic & Blixen. Consistent with the focus on broad generalizability to CPD in SSA, only individuals who are unable to provide informed consent will be excluded. Qualitative methods and thematic analysis will follow procedures outlined in previous work conducted by this team (55-57).
Focus group format: Up to 16 adult (≥ age 18) family members of individuals with CPD will be invited to participate in 2 focus groups conducted by Dr. Kahabuka and trainees at the Tanzania site. Family members will all have regular contact with patients (contact a minimum of 3 days/week). Family member focus groups will comprise 6-10 individuals each, and will last up to approximately 90 minutes. Focus groups will be audio-recorded and transcribed verbatim and supplemented with the addition of copious field-notes. Up to 16 health workers will be invited to participate in 2 additional focus groups, using similar format as the family focus groups. Health workers (nurses, doctors, social workers, pharmacists) will be recruited from clinic and hospital-based settings and have experience interacting with patients with CPD.
Individual interview format: Up to 15 patients with CPD will be interviewed regarding barriers and facilitators to medication adherence. Data recording will be the same as with focus groups.

Phase 2
In Phase 2/Aim 2, informed by the mixed-methods data from Phase 1, the study team will adapt the CAE-L intervention to be culturally and linguistically appropriate for the Tanzanian setting. The “deliverable” of Phase 2 will include a manualized intervention that combines a psychosocial intervention to promote adherence + use of LAI.

Phase 3
In Phase 3/Aim 3, the study team will select appropriate measures, train staff in measure implementation, and finalize CAE-L for delivery. Social worker interventionists will be trained to deliver CAE-L. Finally, the study will roll-out and evaluate CAE-L in 20 individuals with CPD in a 6-month (25-week) prospective training/proof-of-concept exercise. CAE-L will be further refined based upon input from interventionists and study participants. The “deliverable” of Phase 3 will include building capacity of a clinical trials infrastructure that includes identification of relevant tools/ measures and appropriately trained staff who are capable and available to conduct research to improve health outcomes for people with CPD in Tanzania.

Phase 3 Study Population:
The study will enroll 20 adult patients with the following criteria:
Inclusion Criteria:
1. Individuals age 18 and older with schizophrenia or schizoaffective disorder.

2. Known to have medication treatment adherence problems as identified by the TRQ (20% or more missed medications in past week or past month)
3. Ability to be rated on psychiatric rating scales.
4. Willingness to take long-acting injectable medication
5. Able to provide written, informed consent to study participation.

Exclusion Criteria:

1. History of allergy or intolerance to haloperidol or haloperidol decanoate.
2. Individuals on long-acting injectable antipsychotic medication immediately prior to study enrollment.
3. Medical condition or illness, which in the opinion of the research psychiatrist, would interfere with the patient's ability to participate in the trial.
4. Physical dependence on substances (alcohol or illicit drugs) likely to lead to withdrawal reaction during the course of the study in the clinical opinion of the treated research psychiatrist.
5. Immediate risk of harm to self or others.
6. Female who is currently pregnant or breastfeeding.

A Screening Form for each patient will be completed regardless of whether the patient is ultimately enrolled. The form will detail reasons for exclusion, allowing an estimate of sample generalizability. All study procedures will be conducted at Muhimbili Hospital and its associated ambulatory clinics.

LAI: Patients on oral haloperidol will be switched to haloperidol decanoate as per manufacturer's package insert. Individuals not on antipsychotic medication at the time of screening assessment or who are on a different antipsychotic medication, will receive an oral tolerance test (OTT) consisting of up to 14 days of oral haloperidol 2-5 mg twice daily. If the OTT suggests good tolerability, the participant will then receive LAI (haloperidol decanoate) intramuscularly after completion of baseline assessments. Dosing of LAI will be as clinically indicated using conservative dosing to minimize drug-related adverse effects. In the CWRU studies, mean end-point dose of haloperidol decanoate was 68.0 mg, SD 21.1, Range 50-100 mg/monthly injection. It is anticipated that patients will continue on the same dose for 6 months, although dose changes will be permitted based upon clinical status. Each study participant will receive up to 8 injections during the study.

Concomitant treatments: Stable dose psychotropic drugs (> 30 days of previous use) other than antipsychotics will be continued. New psychotropic medications will be strongly discouraged. Medications for side effects may be given at the discretion of the treating psychiatrist and their use will be recorded.

CAE: CAE targets key areas relevant to adherence in CPD: 1.) inadequate understanding of mental disorder, 2.) lack of adequate medication-taking routines, 3.) poor communication with care providers and 4.) substance use which interferes with adherence and recovery. CAE delivered components are selected based upon findings from the ROMI and AMQ. Additional adherence barriers relevant to Tanzanians with CPD and the intervention and assessment tools will be adapted accordingly. CAE will be delivered in approximately 8 sessions by a social worker interventionist, ideally at the same time that LAI is administered.

Study Measures: Baseline information will include previous illness history including duration of psychiatric illness, past hospitalizations, suicide attempts, medication treatment history and cumulative medical burden as evaluated by the self-reported Charlson Index. Table 1 illustrates Phase 3 schedule of procedures. Primary outcomes will be change on TRQ and mean LAI injection frequency. Secondary outcomes will include additional information on adherence attitudes (DAI), CPD symptoms (BPRS, CGI), and Social functioning (SOFAS). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and Alcohol Use Disorders Identification Test (AUDIT) (53) will assess substance use. All outcome assessments will be conducted at study baseline, Week 13, and at Week 25 follow-up.

Safety/Laboratory Evaluations: Safety evaluations will include basic laboratory evaluations (serum comprehensive metabolic panel, lipid profile, CBC with differential, and HIV as well as urine pregnancy testing for women) and EKG. Patient vital signs and weight will be collected at each study visit. Standardized measures of extrapyramidal symptoms will be assessed with the Extrapyramidal Symptoms Scale-Abbreviated version (ESRS-A). Finally, reported side effects will also be evaluated at each study visit using a standardized form developed in the CAE-L studies conducted at CWRU

Study Procedures: Procedure timing is outlined in "Table 1: Phase 3 Schedule of procedures."

Phase 3 Study Measures:
Baseline information will include previous illness history including duration of psychiatric illness, past hospitalizations, suicide attempts, medication treatment history and cumulative medical burden as evaluated by the self-reported Charlson Index. Table 1 illustrates Phase 3 schedule of procedures. Primary outcomes will be change on TRQ and mean LAI injection frequency. Secondary outcomes will include additional information on adherence attitudes (DAI), CPD symptoms (BPRS, CGI), and Social functioning (SOFAS). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and Alcohol Use Disorders Identification Test (AUDIT) (53) will assess substance use. All outcome assessments will be conducted at study baseline, Week 13, and at Week 25 follow-up.

Primary Outcome:

Treatment adherence behavior will be evaluated with the self-reported Tablets Routine Questionnaire (TRQ) and adherence with regular LAI injections. The literature on measurement of treatment adherence, including the PI's work in this area (Sajatovic 2004, Sajatovic in Press-a, Colom 2005) recommends multiple-method assessments to fully characterize treatment adherence. A total combined adherence score (proportion of medications taken out of total medications prescribed) will be calculated as an average of the TRQ values of all orally-prescribed medications. LAI injection frequency will also be assessed.

The Tablets Routine Questionnaire: (TRQ) (Scott 2002, Peet 1991) has been noted by other investigators to be reliable and appropriate for use in seriously mentally ill populations (Peet 1991, Scott 2002). The TRQ determines proportion of prescribed medication taken and is not dependent upon timing of medication provided that medication is consumed within the required day/24 hour period. This rating has demonstrated statistically significant association with past non-adherence, repeated past non-adherence, any non-adherence in the past month, and non-adherence in the past week ($X2=7.2$, $df=6$, $p=.03$). Compared with non-adherence in the past two years, missing 30% or more of prescribed mood stabilizers in the past week has a specificity of 100% and a sensitivity of 65%. Compared with non-adherence in the past week, it has specificity of 87% and a sensitivity of 84% (Scott 2002). The TRQ format will be modified slightly to document all adherence values (an exact proportion) for each item.

LAI Injection Adherence: LAI injection adherence will be determined as a proportion of LAI (paliperidone palmitate or haloperidol decanoate) injections received at the appropriate time (within 7 days of scheduled time).

Secondary Outcome:

Adherence Attitudes: The Drug Attitude Inventory (DAI), is used to measure attitudes towards medication among individuals with serious mental illness (Awad 1993), and is known to be relatively unaffected by psychiatric symptom severity (Sajatovic 2002). The DAI was originally developed to assess the attitudes and subjective experience of patients with schizophrenia being treated with antipsychotic medications and has also been widely utilized with other seriously mentally ill populations receiving psychotropic medication (Sajatovic 2003). The 10-item version of the scale will be utilized (Awad 1993). The DAI is a simple, true-false format questionnaire that assesses domains of patient's attitudes including positive and negative experience, locus of control, and attitudes towards health. Responses are scored on a euphoric-dysphoric continuum (alpha= 0.93).

Symptoms: Symptoms of schizophrenia and schizoaffective disorder will be addressed using the Brief Psychiatric Rating Scale (BPRS) developed by Overall and colleagues (1962).

The BPRS, developed by Overall and Gorham (1962), is a widely used, relatively brief scale that measures major psychotic and non-psychotic symptoms in individuals with SMI. The 18-item BPRS is

well-validated and is perhaps the most researched instrument in psychiatry. Reliability coefficients are reported to be in the range of 0.56-0.87.

Global psychopathology: Global psychopathology will be measured with the Clinical Global Impressions (CGI) (Guy, 1976) a widely used scale which evaluates illness severity on a 1 to 7 point continuum. Severity of illness ratings on the CGI have reported reliability scores ranging from 0.41-0.66 (Guy, 1976).

Social Functioning: Life and Work Functional status will be evaluated using the Social and Occupational Functioning Scale (SOFAS), which is derived from the GAF. The GAF is a 100-point single-item scale which measures global functioning of psychiatric patients and is widely utilized in clinical studies involving Seriously Mentally Ill patients (Jones, 1995). The reliability of the GAF ranges from 0.62-0.82.

Alcohol and Substance Use: The 10-item version of the Alcohol Use Disorders Identification Test (AUDIT) will be used to asses alcohol use (Saunders et al, 1993). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) will be used to measure drug use (World Health Organisation ASSIST Working Group, 2002).

Health Resource Use: Resources that are typically utilized by the most severely ill individuals with schizophrenia include emergency care and hospitalization. Resource use in the 6-month period prior to study enrollment and in the 6-month study period will be evaluated.

Safety/Laboratory Evaluations: Safety evaluations will include basic laboratory evaluations (serum comprehensive metabolic panel, lipid profile, CBC with differential, and HIV as well as urine pregnancy testing for women) and EKG. Patient vital signs and weight will be collected at each study visit. Standardized measures of extrapyramidal symptoms will be assessed with the Extrapyramidal Symptoms Scale-Abbreviated version (ESRS-A). Finally, reported side effects will also be evaluated at each study visit using a standardized form developed in the CAE-L studies conducted at CWRU (Appendix 4)

Other Outcomes of Interest:
Attitude toward Medication Questionnaire (AMQ): A modification of the Lithium Attitudes Questionnaire, the AMQ evaluates an individual's attitudes towards psychiatric medication. The AMQ comprises 19 items grouped into 7 subscales: general opposition to prophylaxis (4 items), denial of therapeutic effectiveness (2 items), fear of side effects (2 items), difficulty with medication routines (4 items), denial of illness severity (3 items), negative attitudes toward drugs in general (3 items), and lack of information about psychiatric medication (1 item). Higher scores on each subscale represent more negative attitudes toward mood stabilizers.

Rating of Medication Influences (ROMI), is a measure of attitudes towards medication treatment that was originally developed for populations with schizophrenia. For this project we will be using Part II of the ROMI, which contains 10 items that directly inquire about influences leading to non-adherence. The ROMI has been found to be reliable, clinically sound and valid compared with other independent measures of attitudes toward medications and compliance.

Vulnerable populations:
Pregnant Women
If a woman becomes pregnant while in the study, the PI will make a clinical decision as to whether the study drug will be discontinued based on the risk/benefit ratio for use of that specific drug in pregnant women. As with all subjects who discontinue medication early but wish to continue in the study, these women will be permitted to complete the CAE sessions and the remaining study visits.

Major psychiatric illness
Because this is a study evaluating the effectiveness of CAE and long-acting injectable antipsychotic medication on people with schizophrenia or schizoaffective disorder, subjects must have been diagnosed

with one of these major psychiatric illnesses to be able to participate. The capacity to which an individual within this subpopulation is able to give consent may vary from individual to individual. To acknowledge this issue, procedures have been put in place to ensure that each individual is capable of giving signed written consent. A witness who is not part of the study team will sign the consent form to ensure that the study was thoroughly explained to the participant and that they comprehend the study procedures and the associated risks and benefits of participating. Within this subpopulation are also individuals who may have a Legally Authorized Representative (LAR). For these individuals, the signed written consent of the LAR is required in addition to the individual's signed written consent. If an individual is deemed unable to provide signed written consent, they will not be permitted to participate, regardless of the presence of signed written consent from the LAR.

Illiterate individuals
Some participants may be unable to read. In that case the ICF will be read to them in the presence of a witness who will co-sign the consent form.

Non-English speaking individuals
Participants will be residents of Tanzania. All study documents presented to the participants (ICF, surveys, flyers, if applicable) will be translated to Swahili; the research personnel at the study site will be fluent in the local language.

Plan for Obtaining Informed Consent:
Once potential participants have been identified, the purpose of the project will be explained to them, and consent will be obtained. The languages spoken in Tanzania are predominantly English and Swahili. The study team in Tanzania will be fluent in those two languages. The consent forms will be available in both English and Swahili, and the study staff will ask the participant about their preference. Potential participants will be provided with the written copy of the consent form, and the research staff will ask whether the participant has any questions. Individuals with limited literacy may have the consent form read aloud to them. Given the known importance of community and family support in this setting, family members will be encouraged to participate in the information-sharing and consent process in order to allow for patient and family consensus and allow ample opportunity to ask questions and completely understand the research project. If the participant agrees to participate, the researcher and participant sign the consent form. A copy of the signed consent form will be given to each participant. The research assistant will then record that the consent was obtained.

Risks
Phase 1: Patients will not be compelled to participate in any way in the activities of the project. Participants will be free to withdraw from the project at any time without penalty. This study involves participating in focus groups, and completing a set of self-report instruments, along with qualitative interviews. All instruments have been utilized in outpatient research settings and are not associated with risks to patients. The risks to the participants will be primarily those of talking about some matters that they may find uncomfortable. Because of the nature of group interaction, patient confidentiality cannot be guaranteed however, the importance of respecting other group members' privacy will be stressed to all participants.

Phase 3:
Risks to taking haloperidol and injectable haloperidol decanoate may include common side effects such as drowsiness, reduced motivation or reduced interest in daily activities. Other side effects may include dizziness, blurred vision, upset stomach, loss of appetite, headache, drooling, dry mouth, sweating, and sleep disturbances. Most of these are transient and subside over time or with dosage adjustment. Acute extrapyramidal effects such as muscle rigidity or tremor or shaking may occur in some individuals. Other involuntary movements such as tardive dyskinesia can occur with haloperidol or haloperidol decanoate, but are generally associated with longer-term use. Since haloperidol is already the most commonly used antipsychotic medication at the Tanzania site, it is expected that most staff will be familiar with potential adverse effects. Potential risk of medication-related side effects will be minimized in several ways, including: 1.) use of OTT to ensure that participants do not have allergy or

intolerance to haloperidol. Individuals who fail OTT will not receive LAI 2.) use of lowest effective dosage, 3.) regular monitoring for side effects using a standardized tool and assessment at all clinical visits, and 4.) use of agents to manage side effects as appropriate. Blood draw: Risks from taking blood samples and/or receiving the medication injection include fainting, discomfort, bruising, or infection at the blood sample puncture site. Use of staff with expertise in phlebotomy, infection control and intramuscular injection will minimize adverse effects of blood draws.
Changing from one antipsychotic to another: Stopping an antipsychotic medication may cause a return of some symptoms that were under control. For example, stopping antipsychotics may cause insomnia (difficulty sleeping), or the appearance of abnormal muscle movements.
The study doctor may be able to give participants medicine to help control these symptoms.
CAE: The behavioral intervention intended to enhance adherence is not generally known to increase risk to individuals.

Benefits
There may be several potential benefits to the participants. Participants being interviewed may find it helpful to discuss their experience. Some participants may benefit from participation in the sessions and from receiving LAI. There is no guarantee of benefits to any participants. However, haloperidol is an evidence-based treatment for CPD and it is expected that at least some patients may experience symptom reduction. It is the goal of this project to contribute knowledge, which can be useful in improving treatment adherence in participants with CPD. It will be explained to participants that their participation in the study may not benefit them in any way but may be of benefit to other patients in the future.

Data and Safety Monitoring Plan
Tanzanian investigators and research staff will be responsible for all on-site stages of the project: recruiting and consenting participants, conducting the surveys, focus groups and interviews during Phase 1, and conducting all study assessments during Phase 3. They will be responsible for all data collection. Management of data will take place at the Muhimbili Hospital site, but de-identified data will be transferred to CWRU. CWRU will conduct quantitative data analysis.
The data and safety monitoring plan for this project consists of two components, as outlined below. The contact PI (Dr. Martha Sajatovic) in coordination with the Tanzanian site PI (Dr. Jessie Mbwambo) will be responsible for ensuring that this plan is followed during the course of this study.
Component 1: Approval from the UHCMC Institutional Review Board (IRB) and from the Muhimbili University IRB will be obtained prior to performing any research related to this study and approval will be maintained throughout the study period via continuing review.
Component 2: Dr. Sajatovic & Dr. Mbwambo will co-lead regular research staff meetings to closely monitor study start-up and progress, including oversight of staff training and research capacity building. These meetings (held via SKYPE conference will be held approximately every other week for the first 3 months of the project and then at least once a month by web teleconference thereafter. Meeting minutes will be sent to all research staff participants. Regularly scheduled conference calls will be supplemented by more frequent local meetings and ad-hoc meetings that may be called in the event that problems or concerns arise. In addition, there will be 1-2 in-person visits to the sites annually.
Any adverse or unexpected events will be reported in accordance with local IRB requirements.

Statistical Analysis:
Phase 1: First, the qualitative team will first independently review each transcript and highlight significant statements, sentences, or quotes. Based on review of the independently derived statements, the team will develop consensus-based “clusters of meaning” (58) or relevant “themes and categories” (58). Researchers will further read/code each document independently and iteratively until no new insights emerge.
These entries will be elaborated as coding progresses. The qualitative researchers will then construct a consensus-based coding dictionary that includes mutually exclusive definitions for each code. This coding structure will be reviewed after a preliminary analysis of a sub sample
of transcripts, and the dictionary will be refined through comparison, categorization, and discussion (59-60). Then, using data and codes, the qualitative team will create code-based files across all

respondents. The team will further elaborate, refine, and differentiate the codes and identify similarities and differences through comparison of respondents.

Phase 3: Quantitative analysis will be limited as the focus is on feasibility, patient acceptability and research capacity-building. However, we will assess descriptive statistics and change from baseline in the primary and secondary measures using standard pre-post techniques.

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Table 1: Phase 3 Schedule of procedures:

Procedure	Screen*	V1/ Baseline*	V2/ Week 1	V3/ Week 5	V4/ Week 9	V5/ Week 13	V6/ Week 17	V7/ Week 21	V8/ Week 25
Informed consent/inclusion & exclusion assessment	X								
DSM-5 diagnosis of Schizophrenia or Schizoaffective Disorder	X								
TRQ	X	X	X	X	X	X	X	X	X
LAI injection frequency		X				X			X
Demographics	X								
Adherence vulnerabilities: ROMI, AMQ	X								X
Laboratory testing	X								X
EKG	X		X						X
Physician Exam	X								X
Oral Medication Dispensing (if applicable)	X								
Adherence attitudes : DAI		X				X			X
CPD Symptoms: CGI, BPRS		X				X			X
Health Resource Use		X				X			X
Social functioning: SOFAS		X				X			X
Standardized side effects: ESRS-A	X	X				X			X
Alcohol and Drugs: AUDIT, ASSIST		X				X			X
Height (Screen only), Weight, and blood pressure	X	X	X	X	X	X	X	X	X
Comorbidity: Charlson	X								
Pt Acceptability & Satisfaction									X
CAE intervention		X	X	X	X	X	X	X	X
Injection		X	X**	X	X	X	X	X	X
Clinician visit – medication assessment, reported side effects		X	X	X	X	X	X	X	X

* Screening and baseline assessments may be completed in a single visit if it is more convenient for the participant
** May require additional baseline booster injection depending on dosage