Study Protocol

Submitted to Muhimbili University of Health and Allied Sciences (MUHAS) and National Institute of Medical Research – Tanzania (NIMR) IRBs (aligns with approved Duke IRB protocol)

Study Title: Family Psychoeducation for adults with psychotic disorders in Tanzania (NIMH R34, Baumgartner, PI, NCT04013932)

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Protocol Title: **Family Psychoeducation for Adults with Psychotic Disorders in Tanzania (Phase Two--Pilot Clinical Trial of the KUPAA intervention)**

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Research Abstract

A major obstacle to care for those living with psychotic disorders such as schizophrenia globally is an absence of evidence-based practices appropriate for cultural contexts where resources are scarce, families are fundamental for treatment, and where many affected individuals and their families hold traditional (i.e. non-biomedical) ideas about the cause of psychosis and seek treatment from traditional practitioners. Family psychoeducation (FPE) is an evidence-based practice used in high-income countries to help individuals with psychotic disorders and their relatives to cope more effectively with the illness; however, FPE has never been tested in a low-resource country nor have the mechanisms of action for this psychosocial intervention been fully identified in any context. KUPAA is a culturally tailored version of FPE. The goal of this study is to pilot test KUPAA for adults with psychotic disorders and their relatives. KUPAA, being a culturally tailored version of FPE, is appropriate for cultural settings inclusive of both traditional and biomedical ideas about mental illness and that incorporates relatives as co-facilitators of the intervention. Formative research [~80 qualitative interviews] has already been conducted in Phase One. This current Phase Two is a small randomized controlled trial (RCT) with 72 patient/relative dyads that will test the KUPAA intervention to a) assess the feasibility and acceptability of an adapted family psychoeducation intervention for 12 weeks, and b) explore its impact on patient relapse, quality of life and disability. This pilot effectiveness trial will adequately prepare us for a subsequent NIH R01 submission for a fully powered RCT of KUPAA against the standard of care in Tanzania.

Purpose of the Study

While the burden of mental illness in in low- and middle-income countries (LMICs) is now well established, there remains a significant treatment gap for mental disorders, particularly for psychotic disorders in sub-Saharan Africa[1,2,3]. However, a major obstacle to care for those living with psychotic disorders such as schizophrenia in Africa is an absence of evidence-based practices (EBP) appropriate for populations where resources are scarce, families are fundamental for treatment, and where many affected individuals and their families hold traditional (i.e. non-biomedical) ideas about causes of psychosis and seek treatment from traditional healers[4-7]. Given this cultural context, utilizing an EBP developed in a high-income country requires careful adaptation and tailoring and a clear understanding of the change mechanisms of the intervention. In addition, the implementation of a newly tailored psychosocial intervention must complement a country's existing mental health platform and it must have the potential to reach more individuals with psychotic disorders with more effective care and treatment. This study posits that a new culturally tailored model of family psychoeducation—KUPAA—has great potential for improving the reach, quality, and effectiveness of mental health services for those with psychotic disorders in Tanzania and in similar global contexts with some new key features—namely, by using family members as co-facilitators for the FamPE group sessions and addressing the traditional beliefs and practices of affected individuals and their caregivers within the program.

The study is being conducted in two phases and we are seeking ethical approval for Phase Two at this time. [Phase One has Duke eIRB Continuing Review ID CR001_Pro00080044 and the protocol title is "Family psychoeducation for adults with psychotic disorders in

Tanzania (Phase One--Formative Research)". The formative phase addressed Objectives 1 and 2 from the original NIMH grant.

Phase Two –A pilot clinical trial of the KUPAA intervention addresses Objectives 3 and 4 from the original NIMH grant.

Primary study objectives

1) To pretest the quantitative patient and caregiver surveys and KUPAA groups to finalize all study materials and procedures
2) To pilot test the KUPAA intervention to assess its feasibility and acceptability among both patients and caregivers
3) To pilot test the KUPAA intervention to explore its impact on patient relapse, quality of life and disability

Secondary study objectives

4) To elucidate the mechanisms of action for KUPAA (e.g. hopefulness, self-efficacy) and refine the mediation and study outcome measures for a future R01/fully powered clinical trial

Background & Significance

Mental Health Services in Tanzania The United Republic of Tanzania has over 45 million people and only 0.04 psychiatrists per 100,000 persons in the country[8]. With limited human resources, outpatient psychiatric services largely focus on medication management while psychosocial services are rare. The Tanzanian Ministry of Health, Community Development, Gender, Elderly, and Children (MoHCDGEC) endorses mental health services through primary care and it recognizes that familial care and support are crucial. Family involvement in psychiatric care is the norm in Tanzania and family members' perception of illness causality greatly influences treatment choices including antipsychotic medication adherence[9,10]. Likewise, relapse and recidivism (i.e. the "revolving door phenomenon") are unacceptably high among clients of psychiatric services at Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania's commercial capital. MNH offers general mental health education classes on a drop-in basis for outpatients and their families waiting to be seen but there are no formal group services for patients. Likewise, at Mbeya Referral Hospital, one of four higher level referral hospitals in the country, there are no formal psychosocial services beyond ad hoc individual family conferences held for individuals with frequent relapses. These health facilities (our study sites) are two of the best public health facilities in the country and yet they offer no evidence-based psychosocial services for patients with psychotic disorders. KUPAA would complement the existing mental health strategy of the MoHCDGEC and potentially reduce relapse and disability and improve social functioning for affected individuals as well as reduce familial burden and stigma.

Family psychoeducation (FPE) is an evidence-based practice developed in high-income countries that, among other things, educates affected individuals and their families about mental illness so that they may better understand and manage it [11,12]. FPE is a specific type of psychoeducation that includes both affected individuals and their family members together and that can be offered in a group format with multiple families. Research shows that critical ingredients for FPE include education about the illness, information resources, skills training and ongoing guidance about illness management, problem-solving, and social and emotional support[13]. FPE is provided in three phases: 1) joining sessions; 2) an educational workshop with a standardized curriculum; and 3) ongoing sessions. Literature reviews of controlled and comparative clinical trials have shown that FPE reduces relapse and re-hospitalization compared to standard services and recent studies have found positive effects on the functional aspects of recovery such as employment, and social functioning[12,13]. Due to the level of evidence, the Schizophrenia Patient Outcomes Research Team (PORT) includes FPE in its treatment recommendations[14]. The multiple family group FPE format in particular, could be highly appropriate for cultural contexts such as Tanzania where the vast majority of affected individuals live with families, independent living is rare, and problem-solving often involves the larger community (i.e. other affected families, clan support/councils). Multifamily groups are a specific format that can help address social isolation, stigmatization, and psychological burden by strengthening the social support network, providing a forum for mutual aid and problem-solving, and increasing hope through mutual example and experience[15,16].

The KUPAA study would fill an important research gap given that FPE is being promoted as a global best practice without the associated regional evidence or sufficient evidence of the underlying mechanisms of action. Researchers and providers across Africa have discussed the need to integrate biomedical and traditional approaches to more effectively treat mental health problems, but there is little evidence for how to accomplish this integration[17-20]. FPE has the unique potential to be a culturally relevant and flexible intervention given the program's design which could allow for incorporating multiple perspectives on health and healing. There is ample evidence that culturally centered interventions improve patient outcomes[21,22]. We posit that a culturally tailored FPE model that explicitly addresses biomedical and traditional perspectives will have a positive impact on service engagement and the recovery process for adults with psychotic disorders in cultural settings where populations hold traditional beliefs. This research could contribute valuable information for U.S. populations who similarly hold traditional beliefs and utilize alternative, non-biomedical mental health treatments.

Family Members as Co-Facilitators of KUPAA. In addition to adapting the educational content of the original FPE model, the proposed KUPAA study would be testing a model of FPE whereby family members of individuals with psychotic disorders are trained to be co-facilitators of the KUPAA groups. Two facilitators are needed to run groups which can be resource intensive for many health facilities in Tanzania. Therefore, using trained and motivated relatives as co-facilitators would address human resource concerns, but more importantly, there is significant evidence of the positive impact of familial peer-support on family outcomes and peer support more broadly for affected individuals[23-25]. Relative co-facilitators have not been specifically tested for the FPE model anywhere globally including the U.S.; however, a recent study in China found that family-led peer support groups with psychoeducation content resulted in positive outcomes for both patients and families[26]. In countries where mental health providers are scarce, this model has important implications for sustainability. Likewise, in the U.S. where FPE is underutilized and

treatment plans for individuals with severe mental illnesses often struggle to engage supportive family members, this model of family co-led FPE groups could provide evidence of a new strategy for engaging families in care[23,27].

Building the Evidence Base for FPE & Mechanisms of Action This project will pilot test a culturally tailored FPE model for individuals with psychotic disorders and their relatives in Tanzania—KUPAA (which means 'to soar' in Swahili). KUPAA will be developed based upon the U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA) Family Psychoeducation Evidence Based Practice KIT[28]. The educational content delivered in standardized curricula focuses on a biopsychosocial perspective for cause, course and management of illness with a few examples of programs that address cultural aspects [13,29,30]. An adapted FPE model that explicitly incorporates biomedical and traditional perspectives could influence the therapeutic efficacy of FPE and lead to better patient outcomes compared to usual care[31-33]. In addition, while some U.S. studies have shown that (biomedical) insight into one's illness is correlated with treatment adherence and illness outcome, there is limited and mixed evidence about how helpful insight is for individuals in settings with strong traditional ideas about mental illness [34-40]. Given the considerable diversity of traditional healing practices in Tanzania and globally [9,41], KUPAA would not focus on a particular traditional belief or practice, but rather how to address multiple health and healing perspectives into the educational component of an evidence-based practice.

There is currently no scientific evidence on the mechanisms of action for FPE in the U.S. This pilot study will explore two hypothesized primary mechanisms of action: adherence to medication/care plan (treatment engagement enhanced when patients can confide in their dual treatment practices) and hopefulness for recovery (resulting in patient resolve to improve functional outcomes and familial support). Additional secondary mediators will also be explored.

Design & Procedures

This pilot RCT will determine the feasibility, acceptability, and preliminary efficacy and mechanisms of change of our adapted KUPAA intervention. KUPAA has not been previously tested in Tanzania, and thus we believe a control group is necessary to determine whether KUPAA is a feasible and efficacious alternative to usual care among this patient population. The RCT design allows for more formal statistical exploration of hypothesized mechanisms of change. Data will be collected at three time points **(baseline, 3 months, 6 months)**, allowing us to assess patient and relative outcomes over time and also assess the feasibility of recruiting, enrolling, and retaining study participants. The pilot study will inform the R01 by allowing us to implement and evaluate our assessment measures, assess the fidelity of KUPAA to core Family Psychoeducation elements, assess acceptability among participants and providers, and assess the hypothesized direction and strength of potential mediators/moderators of the KUPAA treatment-outcome association.

KUPAA Intervention

The formative research of Phase One (Duke IRB Pro00080044) resulted in a draft manual of the KUPAA intervention ready for testing in Phase Two via a randomized pilot clinical trial. KUPAA is based on the SAMSHA evidence-based Family Psychoeducation model, culturally adapted and tailored for a low-resource setting. Each KUPAA group will have 6 patients and 6 matched relatives plus two co-facilitators (one professional and one trained family caregiver). **Professional or practitioner facilitators shall include psychiatrists, clinical psychologists, mental health/psychiatry nurses and medical social workers with experience in mental health care employed at the study facilities. Trained family caregivers will be co-facilitators and shall a task-shifted volunteer who is a primary care giver identified by a client with a psychotic disorder who is accessing out-patient care at either the Muhimbili National Hospital in Dar es Salaam or the Mbeya Zonal Referral Hospital in Mbeya.**

KUPAA is composed of three key services:

1-2 Joining sessions [~30 to 45 minutes each] involve eligible patients and the family member or other individual who the patient has selected. The professional facilitator will meet with the patient for the first joining session and then with the selected family member and the patient together during the second sessions. The joining sessions are important because they give the facilitator and participant a chance to get to know each other before the KUPAA groups begin. They also allow time for the participant and family member to ask questions. The joining sessions will focus on the following.

- A brief review and explanation of the KUPAA model
- Precipitant of current and/or past acute episodes of illness.
- Prodromal signs and symptoms.
- Coping strategies and strengths
- Family and social support
- Assess assets and strengths
- Grief and mourning in relation to the illness
- Treatment goals and planning
- Time for the person to ask questions

Educational Workshop [1 day] will involve family members and eligible patients as determined by practitioners after the joining sessions. The interactive, one day long, workshop will offer information about biological, psychological and social aspects of mental illness; the nature, effects and side effects of psychiatric treatments; what families can do to help recovery and prevent relapse; and guidelines for managing mental illnesses.

12 Family psychoeducation group sessions [~1.5 hours each session] occur weekly in multi-family groups. These sessions follow an empirically tested format and focus on solving problems that interfere with treatment, illness, and symptoms management and that support coping skills and personal care. Case management may also be provided during the sessions and information regarding other mental health resources may also be provided as required by participants.

Study Sites & Standard of Care

The study sites will be Dar es Salaam and Mbeya regions in Tanzania and the collaborating organization is Muhimbili University of Health and Allied Sciences (MUHAS).

MUHAS is co-located with our first study site, ***Muhimbili National Hospital (MNH),*** the national referral hospital, in Dar es Salaam with a catchment area of ~4 million people. The Department of Psychiatry at MNH provides inpatient and outpatient care, has a bed capacity of 70, and admits ~3-10 inpatients per day. Staff includes psychiatrists, psychiatric nurses, social workers, psychologists and occupational therapists. Clinical staff from MNH and academic staff from MUHAS work together per an MOU between these two institutions. All staff participate in teaching and clinical activities and almost all participate in research activities. General ad hoc drop-in psychoeducation sessions for patients and relatives are conducted before commencement of daily clinics and as the need arises. The MNH Department of Psychiatry offers medication management to outpatients with psychotic disorders and psychoeducation by nurses/social workers who discuss one main topic per month with outpatient attendees. On average, 30 participants (mostly patients but also relatives) typically attend these public 30-45-minute sessions and there is a question/ answer period for attendees. Educational emphasis is often focused on involving patients in activities of daily living with social integration being a key indicator of recovery. Clients are also reminded of the importance of follow-up clinics, actions to be taken for missed appointments, signs of relapse, and medication side effects and measures to be taken if encountered. The sessions are not personalized.

Our second study site is ***Mbeya Zonal Referral Hospital (MZRH),*** situated in Mbeya city, 900 km from Dar es Salaam and 100 kilometers from the Tanzania- Zambia border. It is the only referral facility in the southern part of the country with 8 districts with a total population of ~2 million. It is also a referral facility for the neighboring regions. The Psychiatry and Mental Health unit has a 24-bed capacity with an occupancy rate rarely less than 100%. There are male and female wards with 16 and 8 beds, respectively. Major ward rounds are held twice a week and outpatient clinics are held three times a week. Department staff include one psychiatrist, general practitioners, psychiatric nurses, and social workers. Currently, staff conduct individual family conferences only for patients with frequent relapses and more than three admissions in a year. The number of conferences ranges from 3-4 per week. There are no regularly offered psychosocial services for clients with psychotic disorders. There are 50-60 inpatient admissions per month.

[Note: Records from MNH reveal ~1000 adults hospitalized per year in the Department of Psychiatry (~ 1/3 for non-organic psychotic disorders). For MZRH, they admit ~55 new inpatients per month (roughly 1/3 for psychotic disorders as well). Outpatient client numbers are much higher for both sites. We anticipate no problems reaching our target sample sizes using these high-volume clinic sites.]

At each of the clinical study sites, outpatients attending the psychiatric clinics who have a diagnosed non-organic psychotic disorder (each with a matched relative to form a dyad) will be recruited into the Pilot RCT. Outpatient participants will be excluded from consideration if they are younger than 18, older than 50, or have a comorbid developmental disorder with cognitive impairment that would render them unable to give informed consent. Individual randomization will occur at the site level. For Dar es Salaam (MNH site), a target of 24 outpatient/relative pairs

will be assigned to assigned to KUPAA and 24 outpatient/relative pairs will be assigned the standard of care (control group). For Mbeya (MZRH site), a target of 12 outpatient/relative pairs will be assigned to assigned to KUPAA and 12 outpatient/relative pairs will be assigned the standard of care (control group). During recruitment and enrollment, potential study participants must agree to be randomized in order to participate in the study.

Pre-testing recruitment and sample size

The site-specific study coordinators and research assistants (RA) will purposely recruit the pre-testing participants to represent a range of characteristics by age, sex, type of relative/caregiver, length of illness as much as feasible. The team will also allow those who self-identify as being inter7sted (e.g. patient advocates).

Pre-testing surveys with 40 patient and relative participants • 10 patients + 10 relatives-Dar • 10 patients + 10 relatives-Mbeya
Pre-pilot KUPAA groups/training & final revision of training tools • 1 group-Dar (~1x/week for 4 weeks) o 4-6 patient/relative pairs • 1 group-Mbeya (~1x/week for 4 weeks) o 4-6 patient/relative pairs

In order to finalize the KUPAA manual, the team needs real-time feedback on a few KUPAA sessions with patients and relatives. Each site will conduct an abbreviated KUPAA intervention with up to 4 sessions. KUPAA facilitators and participants will share feedback on the process of joining, reception of the educational content, structure of the groups, and other elements of the group process with the team as they finalize the logistical details in the manual. Pretesting the surveys entails being administered all or parts of the survey and sharing with the interviewer their understanding of particular questions as needed. Pretesting also allows the interviewers to test skip patterns, and other logistical issues of administering the survey (flow of sections could be revised based on interviewer feedback from pretesting).

The pretesting of the surveys, but not the pre-pilot groups, will be recorded with the permission of the participants. Recordings will be transcribed by either study staff at the Tanzania sites fluent in Swahili who will transcribe and translate transcripts into English, and/or by a translation service hired by the Tanzanian sites. Transcripts will be shared through the project's sensitive Duke Box folder.

Pilot Clinical Trial recruitment and sample size

For the pilot randomized clinical trial (RCT), we have a study brochure (attached) that explains the study including what it means to be randomized. These brochures will be posted at both study sites around the psychiatry departments and pharmacies where patients pick up their medications. RAs give also general announcements about the study in the outpatient waiting areas. During enrollment, RAs will be situated onsite at the clinics during busy outpatient clinic hours to identify potential participants. This method has worked for previous research projects between

Baumgartner and Kaaya. We estimate that recruitment will take 1-2 months for each site concurrently.

To improve the external validity of our pilot RCT findings, we will seek to enroll outpatient participants with roughly equal distributions across sex, age group and length of illness. Our RAs will keep a roster of the participant IDs with basic demographic data as they recruit so they can purposefully recruit a diverse sample representing women/men, younger/older ages, and recent/chronic illness. The KUPAA treatment groups can start with slightly staggered timing as the target numbers per group are reached. (See attached CONSORT flow diagram).

To enhance retention in the pilot RCT, which is critical, we will call and reach out to participants on a monthly basis to touch base because the data collection time points are three months apart **(0, 3, 6 months).** "Touching base" would be a very brief phone call to ask the participant if this phone number is still valid (it is common in Tanzania to share phones and they may want to designate a new primary contact number), if any other contact information (secondary phone numbers, home address) has changed, and if they have any questions about the study. If we are unable to reach a person via phone, we may plan a brief home-based outreach visit. During the informed consent process, we ask permission for these additional points of contact to help keep participants engaged in the study, particularly the control group who will not be seen as often at the clinics. In a recent NIMH HIV-related randomized trial conducted by Kaaya and Baumgartner in Tanzania, we used this monthly reach out method and found it extremely useful for keeping participants engaged in the research.

Pilot study participants will be assessed three times: baseline (pre-intervention), at 3 months (end of the intervention), and **at 6 months (3 months after the intervention).** After recruitment but prior to the first KUPAA joining session, separate baseline interviews will be conducted with outpatients and their matched relatives (N=144; 72 outpatients and 72 relatives). Follow-up interviews with participants will be conducted 3 and **6 months later**. The 3-month assessment at the conclusion of the intervention will include additional focused feedback related to KUPAA participation for the treatment group. A research assistant will administer all the patient assessments in one session except for the clinician-rated PANSS[71] which will be scheduled for a separate interview within the same week by a co-investigator (Swai or Lawala) who will have received training on its use. Relative interviews are brief and separately administered. In addition to the assessments, facilitators will document KUPAA group attendance and capture qualitative notes on participation (ex. whether patients/relatives are speaking/sharing in the group) and group dynamics. This information may be useful in assessing qualitative differences in FamPE groups and potential for effect measure modification of KUPAA group characteristics on the treatment-outcome associations, which will be more formally estimated in a future R01 (e.g. potential differences by sex in how women and men participate in and benefit from KUPAA).

Selection of Subjects for the Pilot Clinical Trial

We will implement a pilot RCT to determine the feasibility, acceptability, and preliminary efficacy and mechanisms of change of our adapted KUPAA intervention. KUPAA has not been previously tested in Tanzania, and thus we believe a control group is necessary to determine whether KUPAA is a feasible and efficacious alternative to usual care among this patient population. The RCT

design allows for more formal statistical exploration of hypothesized mechanisms of change. Data will be collected at three time points (baseline, 3 months, **6 months**), allowing us to assess patient and relative outcomes over time and also assess the feasibility of recruiting, enrolling, and retaining study participants.

For the KUPAA pre-testing groups, participants can be more purposefully selected as noted in the section "Design & Procedures". Criteria for the pilot clinical trial are noted below.

For patients, inclusion criteria are:

- Attending outpatient psychiatric services at Muhimbili National Hospital or Mbeya Referral Hospital.
- ICD-10 Diagnosis of a non-organic psychotic disorder:
    - F20 Schizophrenia
    - F21 Schizotypal disorder
    - F22 Delusional disorders
    - F25 Schizoaffective disorders
    - Comorbid diagnoses are acceptable for inclusion such as F12.15 'Cannabis abuse with psychotic disorder' as long as they have a primary of F20, F21, F22 and F25
    - Because patient record keeping at Tanzanian psychiatric clinics is variable, diagnostic eligibility will be confirmed by the core study team (PI-Kaaya; Co-I Swai and Co-I Lawala) who are all psychiatrists
- Age 18-50 at the time of informed consent
- Hospitalization or relapse (confirmed by attending psychiatrist or medical officer) within the past 12 months. Because patient record keeping at Tanzanian psychiatric clinics is variable, diagnostic eligibility will be confirmed by the core study team (PI-Dr. Kaaya; Co-I Dr. Swai and/or Co-I Dr. Lawala) who are all psychiatrists.

For patients, exclusion criteria are:

- Younger than 18 or older than 50 at time of consenting process
- F23 Brief psychotic disorder
- F28 Other psychotic disorder not due to a substance or known physiological condition
- F29 Unspecified psychosis not due to a substance or known physiological condition
- Epileptic psychoses
- Bipolar disorder and mania
- If initial diagnosis is substance-precipitated psychosis such as "cannabis induced psychosis", patient would have to be reassessed and given a new primary diagnosis if they are to be included in the study
- Co-morbid developmental disorder, dementia, or other severe cognitive deficit that renders the individual unable to provided informed consent.

Eligibility criteria for caregiver/relatives:

- Age 18 or older at time of consenting process
- Patient agrees that this person can be their paired partner for KUPAA if the pair is randomized to the intervention group

- Typically, the caregiver is a relative as these persons usually accompany patients to clinic and they represent a range of relationships (parents, siblings, spouses); however, a non-relative caregiver is also possible (e.g. guardian, close friend with whom outpatient lives)

Randomization will be the responsibility of the Duke team (Baumgartner, Egger and Headley). After a patient participant is enrolled, consented and administered the baseline survey, the Tanzania team will communicate the participant's study ID, sex, age, and length of mental illness. Once all patients are enrolled (1-2 months), the Duke team will randomize all patients to one of two study arms in equal allocation. Randomization will be stratified by study site and patient-level covariates will be used in a minimization randomization procedure to improve exchangeability across study arm. Results of the randomization will then be communicated with the patient and their paired relative after randomization and before the start of the KUPAA intervention via phone or in person.

Subject Recruitment & Compensation

For both study sites (Muhimbili National Hospital and Mbeya Zonal Referral Hospital), study brochures will be posted and distributed at their respective Departments of Psychiatry. Site PIs and study coordinators are available daily in order to field questions from potential participants. In addition to passive recruitment, the study teams will have the brochures available for outpatient services. If the site PIs (Kaaya, Swai, or Lawala) or site study coordinators (Maboja and Ndelwa) identify a potentially eligible participant during the course of their regular clinical duties which include outpatient service delivery, they also will share the study information. The local teams will review their weekly enrollment logs with the PI during weekly conference calls to assess diversity in recruitment. We will aim for diverse representation focused primarily on patient characteristics (age, sex, length of illness) and to a lesser extent type of matched caregiver (parent, sibling, spouse/partner).

For the Pilot RCT: At each interview **(baseline, 3 months, 6 months),** patient and caregiver participants will each receive 7,500 Tsh (~USD 3.50). Patient and caregiver participants who are randomized to the KUPAA group, will each receive 2,500 Tsh (~USD 1.15) to cover transportation each time they participate in a KUPAA session (up to 12 sessions) which will be held at study sites (MNH and MZRH).

For the pre-testing activities: For each individual activity (pre-testing or a practice group feedback session), participants will be compensated 7,500Tsh (~USD $3.50), as compensation for their time and transportation.

- If s/he is only participating in pretesting, s/he will be given 7,500 Tsh.
- If s/he is only participating in the practice group, s/he will be given 7,500 Tsh for each session s/he participates in (up to 30,000Tsh total). Refreshments will also be provided.
- If s/he participates in both pretesting the survey and the practice group, s/he will be given 7,500Tsh for each meeting (up to a total of 37,500Tsh) and be provided refreshments during practice group sessions.

The payment amounts are established per Tanzania's National Institute of Medical Research (NIMR) guidelines. Each person who provides an informed consent will be given a copy of the informed consent form and signed copies will be place in the research file.
No DUHS subjects will be recruited.

Consent Process

Written informed consent will be obtained from all participants.

Subject's Capacity to Give Legally Effective Consent

We will necessarily include individuals with psychotic disorders because this project will eventually pilot an intervention meant to improve their clinical and social functioning. We are only recruiting adult outpatient participants age 18 or older. All participants with psychotic disorders must be stable at the time of the informed consent process as well as later during the interviews. The core clinical members of the study team (three psychiatrists and the psychiatric nurse/study coordinator: Kaaya, Swai, Lawala, and Maboja) will be primarily responsible for determining whether the participants are stable and have the competence and capacity to consent to research participation (i.e. clinically and cognitively able to consent).

As an additional safeguard to ensure that the participants living with psychotic disorders are able to give adequate informed consent, our research team will re-read and go over the informed consent prior to each follow-up interview **(3 and 6 months).**

Patients can have a few days to decide whether they want to participate as long as they come back to the health facilities and talk to the study coordinator. Most patients typically attend outpatients clinics with their relatives about once a month to pick up their medications at the outpatient clinic but we will alllow them to come back another time (within two weeks of initial recruitment discussion with study coordinator) if they need time to think or to bring in a different relative for potential study participation.

The informed consent process is expected to take approximately 20 minutes per person. However, a potential patient participant and relative participant pair may prefer to ask questions and discuss together since we enrolling pairs, hence, the process could take up to 1 hour. Individual participants will be still be given individual time to ask questions and must sign without their respective patient and/or relative present in order to avoid undue influence from the other. Before requesting participants' signature on the consent form, the data collectors will make every effort to ensure that the participants questions have been answered.

Risk/Benefit Assessment

Potential Risks: There are no physical risks for this psychosocial intervention, but there may be some psychological or social risks for participants. The participants with psychotic disorders may feel embarrassed or disturbed by some of the questions regarding their clinical or social functioning during the research interviews. These risks are minimal; however, if a participant at

any time feels upset and our specially trained interviewers cannot reassure them, the best available psychiatric care and counseling is available through our research sites at any time.

Protections Against Risk: The interviewers will receive special training from the investigators regarding special considerations in interviewing about sensitive topics and all interviewers will be trained regarding confidentiality issues. For the further protection of participants, highly trained supervisors (all of whom currently work in psychiatric services) will supervise a representative portion of interviews. Therefore, specially selected, experienced, and highly trained interviewers will conduct the interviews. The risk that an interview might be overheard should be minimized by the study procedure that specifically requires interviewers to conduct the interview in a room or space where there are no other family members present, unless necessary. Likewise, the caregiver/relative interviews will be held away from the matched patient participants. For the purposes of confidentiality, records of all data will be stored in locked files or rooms. Regular training of research personnel about issues of confidentiality helps prevent staff from violating confidentiality.

In terms of psychiatric assessment, there is a slight risk that participants might be disturbed by questions. Mental health professionals will be available to talk with any individual who expresses such concerns. Furthermore, in case there is a danger of harm to self of others, the local PI and the two local co-investigators, who are all psychiatrists, will be available to assess and treat as needed.

Potential Benefits of the Proposed Research to Human Subjects and Others: The potential benefits to the subjects (particularly for individuals with mental illness as well as their relatives) include the opportunity to talk and share their experience with other persons and learn more about psychotic illness. The risks to respondents are minimal and the measures to be taken reduce them even further. Consequently, we believe that the risk-to-benefit ratio is acceptable.

Importance of the Knowledge to be Gained : The findings will be of great value to Tanzania and other settings globally that need evidence-based practices appropriate for populations where resources are scarce, families are fundamental for treatment, and where many affected individuals and their families hold traditional (i.e. non-biomedical) ideas about causes of psychosis and seek treatment from traditional healers. Evidence-based psychoeducation interventions for individuals with psychotic disorders and their families are currently missing from the standard of care in Tanzania.

Costs to the Subject

There is no cost to the subjects for participation in the study

Data Analysis & Statistical Considerations

The outpatient sample size (N=72: KUPAA intervention, N=36; Control Group N=36) is based on the diversity of participants from whom we want information (ex. rural participants from Mbeya region; want to recruit both recent and earlier psychosis onset). Data from the patient's relatives (N=72) will be used primarily as covariates or mediators/moderators in statistical analyses and, as such, will not contribute to overall statistical power. Per NIMH guidance (PAR-11-278), this pilot

study is not powered to estimate precise treatment effects; however, our sample will allow us to rigorously assess issues of recruitment, retention, measurement, and working with families. Furthermore, we believe that we should, in fact, have reasonably high power to estimate preliminary treatment efficacy, as well as to explore the direction and magnitude of potential mediators and moderators of the treatment's effect on study outcomes. For example, assuming we have 61 participants for analysis, representing 15% loss to follow-up, we expect 80% power to be able to detect a mean difference of 1.8 or larger in a primary outcome (WHODAS), with a two-sided alpha level of 0.05 and a standard deviation of the mean difference of 2.5 or smaller. In assessing the difference in mediating factors, such as medication adherence, we will have 80% power to detect a difference in proportions between the treatment and control groups of about 25% in medication adherence, with a two-sided alpha level of 0.05 and a control group adherence rate of 60%. Power calculations performed using PASS v.13[42].

Data Analysis

Refining measures and evaluating the pilot effectiveness study. The pilot study is a patient-randomized equal allocation, two-arm parallel group, longitudinal trial. [Note: The analysis plan is designed with rigor and with an eye towards transparency for a future R01 RCT trial]. Prior to any assessment of change over time in the targeted outcomes, we will investigate the reliability of our primary outcome measures. In particular, 1) the internal consistency of multi-item scales, 2) measurement invariance across important sub-populations and over time, and 3) stability of constructs over the pre-/post-treatment assessment timepoints. These issues will be addressed using exploratory and (when appropriate) confirmatory factor analyses for data collected by survey instruments over the pre-/post-assessments. We will also provide a quantitative description of attrition over the pre-/post-treatment assessments with the aim of identifying the reasons for attrition and evaluating possible threats to internal validity of the intervention effect due to systematic loss of follow up data.

The primary statistical analysis will be based on intention-to-treat principles; however, we will also consider analyses that focus on more restrictive cohorts (e.g., per protocol analysis).[43] Descriptive statistics will be generated to understand the distributional forms of all variables. Tabular and crude analysis of the difference in continuous outcomes between treatment and control groups at **3 and 6 months** will be performed using an independent T-test or Mann Whitney U test. Tabular and crude analysis of the difference in **3- and 6-month** binary outcomes between treatment and control groups will be performed using a Chi-square or Fisher's exact test. All analyses will be performed using SAS Version 9.3 software (SAS Institute, Cary, NC).

Linear and generalized linear mixed modeling will be used to test for differences in Gaussian and Bernoulli-distributed mediator and outcome variables, respectively[44]. This approach has several advantages: 1) all available data are modeled, allowing an unequal number of observations for different participants; 2) as a consequence, the model provides reliable estimates of the intervention effect in the presence of missing data (see below), and 3) it is possible to model and estimate variability and correlation structures over time. Models will include parameters to estimate the overall FamPE treatment effect, as well as to estimate the partial mediating and moderating effects of select covariates.

Regression-based mediation analysis will be used to estimate the mediating effects of select variables on the FamPE-outcome relationship[45]. This will include separate regression models to estimate the associations between FamPE treatment and each outcome, the association between FamPE treatment and the mediator, and the additive effect of FamPE treatment and the mediator on the outcome. We anticipate that mechanisms through exposure to the intervention impacts the outcome will differ across outcomes measured from patients versus relatives and will explore this possibility in our data. Structural equation modeling (SEM) will be used to model more complex and dynamic relationships between FamPE treatment, intermediate variables and study outcomes[46]. However, SEM, as well as regression-based mediation and moderation analyses, generally have low power to detect these intermediate effects, compared with estimation of direct treatment effects. As such, these analyses will be performed, where possible, to estimate the general direction and strength of potential mediators and moderators, and results will be used to inform analyses in a future R01. Crude analyses and regression models will be performed using SAS software. Regression-based mediation analysis and SEM models will be fitted using SAS (Proc MIXED/NLMIXED) and M-Plus software (v7.4), respectively. Due to the relatively low power for some of the analyses much of what we will learn from this pilot study is not directly related to the efficacy of the intervention, but rather is meant to inform a scaled-up impact evaluation based on a larger, randomly allocated sample of patients. For example, although the purposive, non-probability, sampling of patients might limit generalizability, by insuring that all salient dimensions of the population of interest are represented in our small patient sample (women/men, Dar/Mbeya, ages 18-34 and 35-50), we will identify critical issues in the recruitment and retention of subjects as well as in the measurement of the primary outcomes and hypothesized mediators across a potentially heterogeneous population.

Data & Safety Monitoring

NIMH required and has approved a *Data Safety and Monitoring Plan* (attached/uploaded) to which we will adhere. It is inclusive of all study phases—Phase One (formative) and Phase Two (pilot clinical trial). Given that this is a pilot study and for a relatively short time period, NIMH did not request a data monitoring committee.

The risks from participation in the study are considered minimal and there are NIH-approved procedures in place for communicating and handling any potential adverse events (Data Safety and Monitoring Plan). The core study team (PI-Baumgartner, local PIs-Kaaya, Swai and Lawala, and study coordinator-Headley, as well as additional team members) have weekly project management conference calls where we can discuss and respond to participant concerns or safety issues. All study-related communication on unanticipated problems involving risks to subjects or others, interim results, protocol modifications and other information that may be relevant to the protection of subjects will be discussed on a phone or Skype/Zoom call with the local PI: Dr. Sylvia Kaaya. Urgent email communications will be sent out with a read receipt. Any changes to study procedures or amendments will be done across all three IRBs (Duke, MUHAS in Dar es Salaam, MZRH in Mbeya).

The investigators will make all study related documents, including consent forms, readily available for inspection by the study's IRBs and its authorized site monitors, and the Office for Human Research Protection (OHRP). On-site study monitoring will be performed by the study and local

PIs or their designees, to verify compliance with human subjects and other research regulations and guidelines, assess adherence to the study protocol, and confirm the quality and accuracy of information collected and entered into the study database. The study will be conducted in full compliance with the protocol. With the exception of modifications required to eliminate immediate participant safety concerns, the protocol will not be amended without approval from the study PI.

Role of external (to Duke) personnel

Duke will partner with investigators from the Muhimbili University of Health and Allied Sciences (MUHAS) in Tanzania. The study team at MUHAS is led by Dr. Sylvia Kaaya (site PI) and Dr. Praxeda Swai (co-investigator). Dr. Paul Lawala (co-investigator) is based at Mbeya Zonal Referral Hospital (MZRH) which has a subcontract with MUHAS as the second site for the research. Other personnel at MUHAS include Ms. Carina Maboja (senior community nurse and KUPAA facilitator), Joseph Temu (research assistant) and Anna Minja (study coordinator). Other personnel at MZRH include Liness Ndelwa (social worker and KUPAA facilitator) and Eliasa Swata (clinical officer and research assistant). Additional research study staff (TBD) will be hired by MUHAS and MZRH to conduct data collection activities as needed. All study staff based at MUHAS and MZRH will be trained on the protocol submitted to MUHAS for ethical approval. MUHAS (with MZRH) will lead all data collection activities and collaborate with Duke on the activities related to intervention implementation, data collection, and data analysis. Additional co-investigator based at Columbia University (Drs. Ezra Susser, Ellen Lukens and Lisa Dixon) contribute technical expertise.

Recruitment and Informed Consent

All participants (patients, relatives) will provide written informed consent. We will follow local regulatory guidelines regarding age of consent for treatment and research which is 18 years old. We will seek ethical approvals from MUHAS, MZRH and the NIMR.

For patients and relatives, we will screen individuals who are receiving outpatient services at one of two government psychiatric clinics for their interest in participating in the study. We will also approach family members that accompany individuals who are receiving treatment for management of psychotic disorders.

All participants will be informed that participation in the study is voluntary. They will also be informed that their current treatment will not be affected if they decide not to participate in the study. Only after a patient has agreed to participate and has consented, will their caregiver/relative be approached for participation and consented.

Cultural adaptation: The language spoken in Tanzania is Kiswahili. All of our study team is fluent in Kiswahili and all interviews and assessments will be conducted in Kiswahili unless a participant requests to be interviewed in English.

Voluntary participation: All subjects will be specifically told that their participation is voluntary at each step in the protocol. Based on previous research experience in Tanzania, we are aware that this needs to be explained carefully and in a way that is culturally sensitive.

Subjects' compensation: All subjects will be paid a modest amount (7500Tsh; ~$5) for travel and subsistence costs related to their attendance during the study interview only (not for attending KUPAA groups). The payment amount is established per Tanzania's National Institute of Medical Research (NIMR) guidelines. Each person who provides an informed consent will be given a copy of the informed consent form and signed copies will be place in the research file.

Privacy, Data Storage & Confidentiality

Confidentiality of information collected is of fundamental importance. The research team will be trained to adhere to strict confidentiality guidelines. Access to individually identifiable private information about human subjects will only be available to the research investigators at the study site. Management of data will take place at Muhumbili University of Health and Allied Sciences (MUHAS), but de-identified data will be transferred to Duke University. Confidentiality measures and protection of data are described below:

- All interviewers will receive strict instructions about the importance of confidentiality.
- Unique participant IDs will be used for participants and no names will be used on transcripts.
- All interviews will be conducted in a private setting that is convenient for the participant; sufficient time will be allowed to reschedule interviews.
- Any digital tape recordings will be stored in a locked cabinet. Recordings will be destroyed after being transcribed.
- Study data will be backed up onto the local PI's computer on a regular basis. Note that all computer terminals used in this project are housed in secure offices, with password protection and daily antivirus updates provided by MUHAS.
- Written notes and transcripts from the Key Informant Interviews will be maintained on a Duke password-protected secured Box server and will only be shared with research staff. Audio-recordings will not be transferred to Duke Box. Duke Box is a secured version of Drop Box software and has multi-factor enabled authentication for added security.

The risks from participation in the study are considered minimal and there are NIH-approved procedures in place for communicating and handling any potential adverse events (Data Safety and Monitoring Plan). The core study team (PI-Baumgartner, local PIs-Kaaya, Swai and Lawala, and study coordinator-Headley) have monitoring calls where we can discuss and respond to participant concerns or safety issues. All study-related communication on unanticipated problems involving risks to subjects or others, interim results, protocol modifications and other information that may be relevant to the protection of subjects will be discussed on a phone or Skype call with the local PI: Dr. Sylvia Kaaya. Urgent email communications will be send out with a read receipt. Any changes to study procedures or amendments will be done across all three IRBs (Duke, MUHAS in Dar es Salaam, MZRH in Mbeya).

Illustrative KUPAA Timetable for Education Workshop

Date	Time	Major Activity	Sub Activities	Responsible person/people
02/May/2019	09.00-09.05 AM	**Introduction and getting to know one another**	Facilitators introducing themselves to the KUPAA group	Facilitators
	09.05-09.50 AM		KUPAA group Introduction - NAMWEZA naming activity	Participants and Facilitators Strategy: **NAMWEZA 3.7.5**
	09.50-10.05 AM	**TEA BREAK**		**INSTITUTIONAL CATERER**
	10.05-10.35 AM	**Norms of the Group Sessions**	-Facilitators to mind map words respect, trust, confidentiality to facilitate and guide participants thinking of group norms. -Facilitators to write the agreed norms on a flip chart and keep on board in the KUPAA space	Participants and Facilitators
	10.35-10.50 AM	I**ntroduction of KUPAA**	-Explain the meaning of KUPAA -Explain why do we want to introduce KUPAA in Tanzania	Facilitators
			-Mention topics that will be learnt in KUPAA sessions	Facilitators
	10.50-12.00 AM	**Psycho education on Mental Illness with Psychosis** See manual for topics to be covered	• Definition and causes of mental illness • Signs and symptoms of mental illness – include residual and prodromal symptoms • Treatment of mental illness/treatment options and anticipated duration for symptom control • Acknowledging and overcoming the implications of grieving associated with illness and loss of functioning • Acknowledging and overcoming stigma towards mental illness • Role of alternative healing practices in generating hope and healthy alternative treatment options. • Preventing relapse: Stressors, stress prevention and stress management • Problem solving • Recovery	Facilitators and participants Strategies: Open discussion together, allowing participants to share experiences associated with each topic and facilitator to conclude after each topic.

Date	Time	Major Activity	Sub Activities	Responsible person/people
	12.00-12.30 PM	**Any concern from the participants**	Allow participants: -to ask questions; give comments, and suggestions -Answer questions accordingly	Facilitators and participants
	12.30-1.30 PM	**LUNCH BREAK**		**INSTITUTIONAL CATERER**
	1.30 - 2.30 PM	**Building empathy and empowering group dynamics through looking at stories in our lives that reveal our strength and competence**	Demonstrate Ability Spotting Exercise (6-7 minutes) and facilitate participants to do "ability spotting" in groups of 3 (6-7 minutes each x 3 = 20-30 minutes). Finish on a positive with every friend wearing a chain of abilities, and conclude on importance of thinking positively.	Facilitators and participants Strategy: **NAMWEZA 3.7.1**
	2.30 - 3.00 PM	**Closing and next steps**	Break into groups for the next KUPAA session and reach agreement on day and time for the next and future group meetings Retention strategies: Agree on reminder text messages prior to meeting and review and confirm correct contact mobile phone numbers; Assign "guardian angels" during a closing cycle.	Facilitators and participants
Review session: What went well and what went not so well – List issues for future improvements. **Preparation for next session:** Summarize in one working sheet issues from joining session 1 &2 for the six-patient/care-giver dyads (pages 45 - 49 in Manual Version_02_13_03_2019, keeping in mind issues agreed NOT to be discussed in MF sessions) in preparation for the first problem solving group session.				

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