Protocol Title: A **T**arg**E**ted M**A**nage**M**ent Intervention for Reducing Stroke Risk Factors in High Risk Ugandans (TEAM-U)

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Background and Rationale

Stroke is a neurological condition with rapidly increasing burden in many low- and middle income countries (LMIC), that is associated with high mortality, high morbidity and years of suffering and disability for stroke survivors and families, as well as escalating costs[1-3]. Nearly 10% of global deaths are due to stroke, and this will increase to over 23 million new cases and 7.8 million deaths by 2030.[4, 5] Africa is particularly hard-hit by stroke burden due to rapid population growth, expanding lifespan, patterns of industrialization, adoption of harmful western diets, and increasing prevalence of risk factors such as hypertension, obesity, and diabetes[6, 7]. Approximately 8% of all first-ever strokes worldwide are in Africa[8, 9]. Importantly, a report on stroke in Africa[10] projects a further increase of 10.8% incident stroke cases and an increase of 9.6% in stroke survivors.

In spite of these daunting projections, stroke is often a preventable disorder. Early identification and management of stroke risk factors can greatly reduce stroke burden. The INTERSTROKE study, a 32 country case control trial, found that hypertension is a main risk factor for stroke [7] that is especially prominent among young Africans with stroke.[11] In sub-Saharan Africa, (SSA) stroke is the predominant outcome of elevated systolic blood pressure (BP).[12]

There are few widely used and effective approaches to minimize stroke burden in SSA.[13-15] Given resource constraints, the ideal approach should be practical, low-cost and widely scale-able. Written in response to *PAR-18-835 Global Brain and Nervous System Disorders Research across the Lifespan,* the proposed project builds upon promising pilot work in which this study team developed a curriculum-guided self-management program called **T**arget**E**d M**A**nage**M**ent Intervention (TEAM)[16] designed to help reduce stroke burden in Uganda. Preliminary work suggests that TEAM has excellent participant acceptability and retention over a 6-month period (87.5 %) and is associated with reduced stroke risk factors, including significantly decreased BP, improved serum lipids, and improved glucose control among individuals with diabetes. The study team has also laid critical groundwork and infrastructure to now refine TEAM based upon community stakeholder input and to conduct a prospective, randomized controlled trial (RCT) vs. a generalizable control. The study team includes experts in behavior change, cardiovascular health, medical education, neurology/brain health, and mixed-methods and clinical trials design and implementation.[7, 17-30; 31-35] The team has also established a productive collaboration that includes training the next-generation of brain health researchers.[36]

The proposed 2-phase project will first refine the TEAM intervention to ensure acceptability across a broad range of Ugandans at risk for stroke and then test the effects of TEAM in reducing stroke risk in a 3-site, prospective, 6-month randomized controlled trial (RCT). In line with Fogarty International Center (FIC) and National Institute of Neurological Disorders and Stroke (NINDS) priorities, the proposal will build critical research capacity to support future work in stroke burden reduction.

Aim 1: To refine the TEAM curriculum for optimal acceptability and integration in the Ugandan setting guided by input from stakeholders (patients/family, clinicians, administrators). TEAM refinement (Phase 1 of the overall project) will be guided by the integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) framework which holds that successful implementation is a function of characteristics of the innovation, recipients (patients and providers), the inner and outer contexts (setting /environment), and facilitation support.

Aim 2: To conduct an RCT comparing efficacy of TEAM vs. enhanced treatment as usual (ETAU) in 246 Ugandans (TEAM, N= 123; ETAU, N= 123) at high risk for stroke. Phase 2 consists of an RCT using a Type 1 hybrid effectiveness-implementation design, which rigorously tests the clinical intervention and secondarily gathers data to inform subsequent implementation efforts and research. The RCT will evaluate key primary (systolic BP) and secondary (biological and behavioral) outcomes indicative of stroke risk. H1: Individuals in TEAM will have significantly reduced systolic BP compared to individuals randomized to ETAU. H2: Individuals randomized to TEAM will have greater reductions in serum cholesterol compared to ETAU. H3: Individuals with diabetes randomized to TEAM will have improved glycemic control as measured by serum HbA1c compared to ETAU. Secondary outcomes also include other biomarker variables, stroke knowledge and attitudes, medication adherence and health resource use. We will also explore associations of age, gender, urban vs. rural residential status and stroke history (prior vs. no previous stroke) on TEAM outcomes.

Aim 3: Identify barriers and facilitators to TEAM implementation in order to inform subsequent scale-up and spread using qualitative methods and guided by an implementation conceptual model. As with Aim 1, Aim 3 evaluation will be guided by an i-PARIHS framework. Finally, the project will grow research capacity in stroke risk reduction, training the next generation of brain health investigators in SSA. The project will help establish a sustainable infrastructure that will facilitate future scale-up of TEAM in Uganda. Taken together, the proposed project has substantial public health importance and will provide the prerequisite data and infrastructure needed to help with reducing stroke burden in Uganda and other LMIC countries across the globe.

Study Design
The proposed project is a prospective, randomized effectiveness-implementation trial of **T**arg**E**ted M**A**nage**M**ent Intervention (TEAM. N= 123) vs enhanced treatment as usual (ETAU, N=123) in Ugandans who are at risk for stroke or have had a stroke within the last 5 years.

Study Procedures
In Phase 1 of the project, stakeholder's advisory board (SAB) will be convened across 3 Ugandan sites. The SAB will be composed of up to 15 relevant stakeholders including 3 stroke survivors, 3 individuals with multiple stroke risk factors as defined above, 3 family members, 3 clinicians and 3 administrators who practice in the proposed study enrollment sites. The purpose of the SAB is to refine the TEAM intervention content to meet the needs of patients and professional healthcare stakeholders and suggest how TEAM might best be incorporated into clinical workflow, as well as give guidance and feedback on recruitment methods and advertisements.

Phase 2 of the project will be conducted across 3 Ugandan sites that will enroll a representative sample of Ugandans at risk for stroke (Mulago, Nsambya and Mbarara Hospitals and their associated outpatient clinics). In the RCT portion of the study, 246 participants will be randomized at baseline on a 1:1 basis to receive either TEAM (N= 123) or ETAU (N=123) and will be followed for a total of 6 months. Since stroke is a moderately long-term health outcome (years to decades) that typically occurs in the presence of one or more stroke risk factors, the project will focus on testing whether TEAM can modify well-established short-term biomarkers that predict stroke risk, specifically BP control, serum cholesterol and blood glucose control. Secondary outcomes of interest include additional stroke risk biomarkers, (HDL, LDL, triglycerides) diet, exercise, use of alcohol and tobacco, stroke knowledge/attitudes, stress, and treatment adherence with risk-reducing medications. We will also explore associations of age, gender, urban vs. rural residential status and stroke history (prior vs. no previous stroke) on TEAM outcomes. To help inform future scale-up should RCT findings be positive, we will assess barriers and facilitators to TEAM implementation using both qualitative and quantitative methods.

Participants: Individuals will be referred by clinical providers at the sites and by self-referral in response to IRB-approved advertisements posted at the clinic site and in the local community. We also expect that some individuals might also self-refer by word of mouth after hearing about the project from someone they know.

Inclusion and Exclusion Criteria

	Inclusion Criteria for RCT participant
1.	Age range: ≥ 18 years
2.	At risk for stroke defined by the following: a.) High systolic BP defined as ≥140 mmHg assessed on at least 2 occasions at least 3 days apart and either criterion b or c as noted below: b.) At least 1 other modifiable stroke risk factor including: diabetes, hyperlipidemia, obesity, smoking, problem alcohol use or sedentary lifestyle. Problem alcohol use for screening purposes

	will be assessed with questions on frequency, type of alcohol and quantity consumed. Participants will be classified as engaging in potential problem alcohol use if they exceed the recommended level for safe alcohol intake i.e. more than 3 drinks on average every time they drink, or if they undertook binge drinking (i.e. more than 3 drinks on one occasion in the one month preceding the evaluation).[70, 71] c.) History of stroke or transient ischemic attack within the past 5 years
3.	Able to participate in group sessions
	Inclusion Criteria for Care Partner participant
1.	Age range: from 18 to 90
2.	Able to participate in group sessions
	Inclusion Criteria for Peer Educator
1.	Age range: from 18 to 90
2.	At risk for stroke defined by the following: a.) High systolic BP defined as ≥140 mmHg assessed on at least 2 occasions at least 3 days apart and either criterion b or c as noted below: b.) At least 1 other modifiable stroke risk factor including: diabetes, hyperlipidemia, obesity, smoking, problem alcohol use or sedentary lifestyle. Problem alcohol use for screening purposes will be assessed with questions on frequency, type of alcohol and quantity consumed. Participants will be classified as engaging in potential problem alcohol use if they exceed the recommended level for safe alcohol intake i.e. more than 3 drinks on average every time they drink, or if they undertook binge drinking (i.e. more than 3 drinks on one occasion in the one month preceding the evaluation).[70, 71] c.) History of stroke or transient ischemic attack
3.	Able to participate in group sessions
	Inclusion Criteria for Peer Educator Care Partner
1.	Age range: from 18 to 90
2.	Able to participate in group sessions
	Inclusion Criteria for Clinic Staff
1.	Member of clinic and administrative staff (whether they referred participants to study or not) at the 3 sites (physicians, nurses, health workers, pharmacists).

	Exclusion Criteria for RCT participant
1.	Individuals who are unable or unwilling to provide written informed consent
2.	Individuals who have sickle-cell disease
3.	Females who are pregnant or lactating
4.	Individuals with dementia
	Exclusion Criteria for Care Partner participant
1.	Individuals who are unable or unwilling to provide written informed consent
	Exclusion Criteria for Peer Educator
1.	Individuals who are unable or unwilling to provide written informed consent
2.	Individuals who have sickle-cell disease
	Exclusion Criteria for Peer Educator's Care Partner
1.	Individuals who are unable or unwilling to provide written informed consent
	Exclusion Criteria for Clinic Staff
1.	Individuals who are unable or unwilling to provide written informed consent

Number of Research Participants

No recruitment activities will take place at CWRU. All participants will be enrolled at the 3 Uganda sites.
There will be 15 stakeholder's enrolled in to the stakeholder's advisory board (SAB).
There will be 246 RCT subjects enrolled.
There will also be up to 12 PE and Care Partner Dyads (PEDs).

Finally, study staff will also conduct qualitative interviews with 5 clinic staff at each site (N=15)

Recruitment Methods

No recruitment activities will take place at CWRU. All participants will be enrolled at the 3 Uganda sites.
SAB members will be referred by study investigators, or other colleagues of the PIs who will talk with the potential SAB member and ask if they are interested in talking with the study team. If the potential SAB member is interested, a member of the study team will contact them and make arrangements for them to talk to a member of the study team to determine if they would be a good fit as an SAB member.

Potential PEs and PE care partners will be referred by study investigators or other colleagues of the PIs who will talk with the potential PE and ask if they and their care partner are interested in talking with the study team about the opportunity to be a PED. If the potential PE is interested, a member of the study team will contact them and make arrangements for them to talk to a member of the study team to determine if they and their care partner would be a good fit for the PED role.

Subjects will be recruited in to the RCT portion of the study from the investigators' clinics, community outreach, via word-of-month from other participants and via IRB approved advertisement.

Setting

All research activities will take place at 3 Ugandan sites:

1. Makerere University College of Health Sciences (MakCHS)/Mulago Hospital
2. Mbarara University of Science and Technology (MUST)/Mbarara Hospital
3. Nsambya Uganda Martyrs University (UMU)/Nsambya Hospital

Consent Process

Consenting for SAB members will take place using video conferencing and/or phone and be done by study staff at Makerere University College of Health Sciences (MakCHS)/Mulago Hospital, Mbarara University of Science and Technology (MUST)/Mbarara Hospital and Nsambya Uganda Martyrs University (UMU)/Nsambya Hospital. For SAB members, verbal consent will be obtained instead of written consent, since the SAB meetings will also be taking place remotely.

The informed consent discussion will be conducted with the participant in the language that the individual is most comfortable with, with help of a translator if the need arises. During the consent discussion, the informed consent form will be reviewed and all its contents will be discussed. Each section of the informed consent will be read to the resident and further explained if the need arises. If the individual agrees to participate, he/she will be asked to verbally confirm their willingness to participate.

Consenting for RCT participants and clinic staff will take place in the offices of study staff at Makerere University College of Health Sciences (MakCHS)/Mulago Hospital, Mbarara University of Science and Technology (MUST)/Mbarara Hospital and Nsambya Uganda Martyrs University (UMU)/Nsambya Hospital.

The informed consent discussion will be conducted with the participant in the language that the individual is most comfortable with, with help of a translator if the need arises. During the consent discussion, the informed consent form will be reviewed and all its contents will be discussed. Each section of the informed consent will be read to the resident and further explained if the need arises. If the individual agrees to participate, he/she will be asked to sign the consent form and their willingness to participate in the study will be documented.

If a participant is unable to read, an impartial third party witness will have to be present during the consent process to confirm that the process has taken place. The consent document must be read to the participant and the process documented in the research file. The participant will "make their mark" (f.ex. thumbprint) on the signature section of the consent document, in order to document their understanding. Both the witness and the person obtaining informed consent. Both the witness and the person obtaining informed consent must also sign and date the consent.

RCT Treatment randomization: After obtaining written, informed consent and following all screening and study baseline procedures, individuals in the RCT will be randomized on a 1:1 basis to participate in either TEAM or ETAU. Block randomization with block sizes ranging randomly between 4 and 8 consecutive patients will be employed to ensure that equal numbers of TEAM and ETAU patients occur within strata and are balanced with respect to relevant comorbidity (diabetes and previous stroke). The randomization list will be computer-generated by personnel within the biostatistics core of the CWRU Neurological and Behavioral Outcomes Center who are not members of the study staff.

Phase 1: Intervention Adaptation and Guidance: Building upon strong existing partnerships between members of the study team and healthcare partners in Uganda, the study team will obtain input from a stakeholder's advisory board (SAB) to refine the TEAM intervention content to meet the needs of patients and professional healthcare stakeholders and suggest how TEAM might best be incorporated into clinical workflow. The study team has an extensive track-record of convening similar stakeholder advisory groups for self-management interventions in diverse brain disorders.[16, 73, 74] The SAB will be composed of up to 15 relevant stakeholders including 3 stroke survivors, 3 individuals with multiple stroke risk factors as defined above, 3 family members, 3 clinicians and 3 administrators who practice in the proposed study enrollment sites. Consistent with i-PARIHS framework, stakeholders will represent intervention recipients as well as the inner context and outer context of implementation efforts. Patient, family and clinician/administrator representation will be balanced across recruitment sites. SAB meetings will be held virtually as much as possible. However, in some parts of Uganda, reliable internet access is not widely availability. This may make it difficult for some people to participate in the stakeholder's advisory board (SAB) if it can only be done remotely. Those who do not have reliable internet access will still verbally consent remotely but will attend the SAB meetings in person. Those SAB members who do have reliable internet access will verbally consent and attend SAB meetings remotely. Therefore, we will have blended meetings where some of the participants attend remotely while others may attend physically. There will be 3 video-conference calls during the first 6 months of the project (using Zoom or similar videoconferencing). In the first call, SAB members will review the TEAM curriculum and identify content areas that they feel may need to edited or added. The study team members will then make these modifications to the TEAM intervention manual. It is expected that at least some of the added content will be appropriate for compiling a supplemental content "toolkit" that can be used as needed based on patient needs. In the 2nd meeting, SAB members will review the revised TEAM content and make any additional /final suggestions. In the 3rd meeting, the SAB will be asked to identify strategies that will be helpful to integrating TEAM into clinic workflow. SAB meetings will be audio recorded and assessed qualitatively. Qualitative analyses will follow previous procedures by this team and are further delineated in the Data Management & Analyses section.[31, 75] After Phase 1 is concluded, the SAB will continue to meet annually for years 2-4 and twice annually in year 5. It is expected that SAB input and guidance will continue to assist with optimal implementation and effectiveness of the project include maximizing recruitment and retention of participants and clinician engagement and referrals.

Phase 2: Intervention Testing/RCT

Schedule of study procedures: As noted in Table 1, each RCT research participant will be assessed 5 times: at screening, at baseline, at 13 weeks (after completion of the TEAM group sessions), at 6 months and at 12 months follow-up. Participants will be reimbursed $15 for each quantitative screening, baseline, and 13-week interview and $20 for the final (6-month) interview. All assessments for a single participant will be done by a single rater trained by the proposed study PIs to pre-established and documented reliability standards. It is expected that patient assessment will require approximately 60-90 minutes for the screening assessment and approximately 45-60 minutes for the baseline and three follow-up assessments. Participants will be reimbursed $20 for each qualitative interview.

Qualitative interviews in a sub-set of RCT patient participants and their care partners (TEAM group: 5 patients and 5 care partners at each of the 3 clinical sites (total of 15 patients and 15 care partners; ETAU group: 5 patients and 5 care partners at each of the 3 clinical sites; total of 60 participants) will be conducted at baseline and at 13-week follow up visits.

In addition, the following qualitative interviews will also be conducted:

- One-time qualitative interviews with clinicians who refer patients will be assessed when their patient reaches the 6-month time-point regarding their perception of the intervention
- One-time qualitative interviews with a sample of clinician/ administrators in Year 4 ((N=15 total, 5 at each site) that mirror the questions asked of patients and additionally on how they perceive TEAM as fitting in or being compatible with existing clinic workflow and recommendations on how this might be optimized in future scale-up.
- One-time qualitative interviews with nurse and PED interventionists at each of the sites with respect to comfort with their role in facilitating/implementing TEAM in Year 4
- One-time qualitative interviews with SAB members in Year 5 on how TEAM should best be scaled-up in consideration of these perceptions

In-person activities with study subjects will not occur in either phase of the study until either the CWRU COVID-19 restrictions are lifted or after obtaining permission from CWRU research administration.

Measures: Demographic variables and existing medical burden (assessed with the self-reported Charlson Index[79]) will be evaluated at baseline, prior to study randomization. Baseline medical status will also be evaluated with personal and family stroke history as well as currently prescribed medications. Primary outcome of the RCT will be change in systolic BP from baseline to 6-month follow-up. Additional outcomes of interest will include diastolic BP, cholesterol/lipids and glycosylated hemoglobin (HbA1c) (approximately 5mL of blood is drawn per blood draw), body mass index (BMI), measures that evaluate diet, activity levels, substance use, self-efficacy, stroke knowledge, stress, medication adherence, medication access and health resource use. Quantitative measures will be repeated at 13-week and 24-week (6-month) follow-up except for laboratory testing, which will be conducted only at baseline and 24-week follow-up. Qualitative evaluation will be conducted at baseline and at 13-week follow-up.

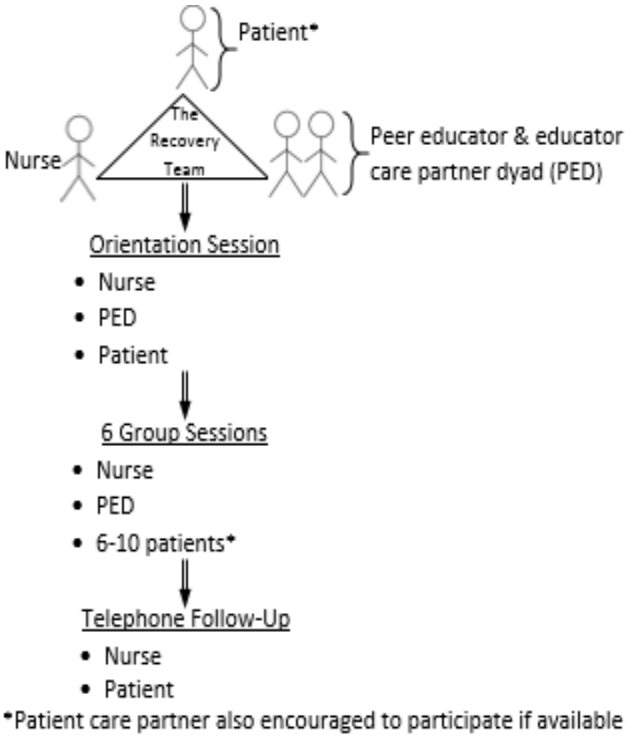
Primary outcome: The primary study outcome is systolic BP measured at baseline, 13-week, 24-week (6 month). All BP measurements will adhere to a standardized procedure previously used by this study team.[30] Prior to BP measurement study participants will be requested beforehand to refrain from smoking and drinking alcohol or caffeinated beverages at least half an hour before the examination. BP will measured with an Omron automated sphygmomanometer model HEM 907 whose accuracy has been validated.[80] The participant will be asked to sit on a chair and rest quietly for 15 minutes with his/her legs uncrossed. The left arm will then be placed on a table with the palm facing upward and the ante-cubital fossa at the level of the lower sternum. Two arm cuffs that fitted arm circumferences 9-13 inches and 13-17 inches will be available for use in BP measurement. Three measurements will be taken at least 5 minutes apart. The average of the last two readings will be considered as the final blood pressure reading.

Secondary quantitative outcomes: Secondary biomarker outcomes will include diastolic BP, serum cholesterol and lipids, HbA1c and BMI. Life-style changes of interest will include diet and salt intake as measured by the modified dietary questionnaire,[81] physical activity as measured by the Global Physical Activity Questionnaire (GPAQ)[82] , tobacco and alcohol use measured by the Global Adult Tobacco Survey (GATS) questionnaire and The Alcohol Use Disorders Identification Test (AUDIT) respectively.[83, 84] To assess risk factor management self-efficacy we will use the General Self-Efficacy measure[81, 85] and stroke knowledge using the same set of questions used in the stroke survey conducted by Nakibuuka and colleagues.[18] As a key focus of TEAM is to encourage engagement and adherence with medical management, we will collect information on medications for stroke risk factors (type and total number). Recognizing that adherence can be intentional or non-intentional we will collect data on adherence via use of a standardized adherence attitudinal measure (Medication Adherence Report Scale /MARS)[86, 87] and query individuals on difficulty (financial or otherwise) in taking medications or medical care. Since our pilot suggested both patients and caretakers reported psychosocial stress, we will assess stress using a combined measure of general stress at home and in the workplace adapting the stress instrument used in the INTERSTROKE study.[88] Twelve months post baseline, we will assess enduring effects of the intervention via a short 5-question survey We will also disseminate information on stress management techniques during stroke education workshops held in the clinics. Additional detail on the stroke education workshops are found in the dissemination description of this proposal.

Qualitative evaluation: To better understand the barriers and facilitators to stroke risk reduction that need to be further integrated into TEAM and evaluate how the RCT sample might compare to the sample enrolled in previous pilot work, the study team will conduct qualitative interviews for individuals who are at risk for stroke. Interviews will use a semi-structured guide adapted from the instrument used in the TEAM study. Qualitative informants will include 15 participants from the TEAM group and their care partners and 30 patients from the ETAU group and their care partners (total N=60). The sample will be distributed in approximately equal proportions across the 3 study sites. We will balance the selection of respondents by age, gender and diabetes comorbidity. The interviews will be audio-recorded, transcribed verbatim, and then translated into English. Final transcripts will have all personal identifiers or specific information that could identify any specific individual removed. The same informants will also be evaluated at the 13-week time point to assess their perceptions of stroke risk factor management, what elements of TEAM or ETAU they might have found particularly helpful, and what could be improved in future efforts targeting stroke risk factor reduction. We will also conduct qualitative interviews with 5 clinic staff at each site (N=15) to derive information on process measures relevant to future TEAM implementation (barriers, facilitators, complementarity with clinic workflow. In Year 4, nurse and PED interventionists at each of the sites will also be qualitatively evaluated with respect to comfort with their role in facilitating/implementing TEAM and in Year 5, the SAB membership will be queried on their perceptions of how TEAM may align with broader healthcare priorities.

TEAM: Similar to previous self-management approaches developed by these investigators[16, 31, 33] TEAM is informed by principles of social cognitive theory.[76] TEAM uses nurses and peer educator dyads (PEDs) composed of patients and their care partners to co-deliver an intervention intended to help reduce future stroke risk (Figure 1). Team begins with one 60-minute 1:1 orientation session, in which the nurse and PED meet with the patient and his/her care partner. This is followed by 6 hour-long group sessions with 6-8 patients and their care partners held approximately weekly. The first orientation session will be done approximately 1 week post baseline, followed by group sessions were done at 2, 4, 6, 8, 10 and 12 weeks post-baseline. Our pilot work suggests that the timing and format of the groups is highly acceptable to participants, with robust attendance/retention. Individuals who miss a group session are encourage to complete a make-up session conducted immediately before or after regularly scheduled groups. In cases where logistic barriers prevent in-person attendance, participants may conduct make-up sessions by phone with the nurse educator. To reinforce learning after the TEAM group sessions are done, 3 brief (approximately 10-20 minute) monthly telephone calls occur between the nurse and the patient over the next 3 months. These calls support ongoing self-management and facilitate linkage with other care providers. All TEAM participants continue in treatment with their regular medical care providers and TEAM visits will take place in these clinics.

Figure 1: TEAM participants and interactions



TEAM Curriculum: Topic content is noted below. In the RCT, content is delivered in 6 sessions.
Session 1: Orientation and introductions, Emphasize ground rules, Establish a therapeutic relationship, Discuss facts and myths about stroke, Overview and interactive discussion of stroke risk factors
Session 2: Medications to manage complications and reduce future risk, Nutrition for best physical and emotional health, Healthy cooking and use of salt in food preparation
Session 3: Problem-solving skills and the IDEA approach (**I**dentify the problem, **D**efine possible solutions, **E**valuate the solutions, **A**ct on the best solution), Effects of exercise, smoking and other substances in recovery
Session 4: Medication routines, acknowledgement of group progress, self-management and recovery as a lifestyle.

Session 5: The importance of having a regular healthcare provider, Talking with health care providers, Working with traditional healers
Session 6: A personal care plane to take care of the body and mind, Acknowledgement of group progress, Self-management and recover as a lifestyle

Training for TEAM: The team will hire and train up to 8 nurses and up to 12 PEDs. Training will follow the same procedures as in the TEAM Uganda pilot and in past self-management trials.[77] Initial training will be a 2-day intensive to review the TEAM curriculum followed by training /support sessions monthly during year 1, at least quarterly thereafter, attended by clinical research staff, nurses and PEDs.

ETAU: ETAU will consist of an orientation visit (approx. 30 minutes) with a nurse who will provide patient-education materials on stroke risk adapted from the American Heart Association materials and cover common risk factors such as hypertension, obesity, high salt/high fat diet and diabetes. This visit will take place in the outpatient clinic where patients get their medical care. Patients will also receive basic written information in their language of preference and tailored to the reading level of most patients at the clinic. Patients will be offered the opportunity to bring a family member with them to this visit who may also ask questions and who can assist them with understanding written materials for those with limited literacy. To control for the same number of patient contacts as TEAM, the nurse in ETAU will then follow-up with participants with a series of 9 brief phone calls spaced out over the course of 6 months (approximately every 2 weeks during months 1 and 2, then approximately monthly thereafter). Content will reinforce materials provided in the orientation visit and the nurse will be available to answer questions that may arise. Different nursing personnel will deliver the TEAM and ETAU interventions to minimize chance of contamination across study arms.

Feasibility and Fidelity: Attendance for each TEAM and ETAU contact will be recorded. Acceptability for each intervention will be assessed at 13 weeks with a brief self-rated survey. Following Fraser et al.,[78] fidelity to the TEAM intervention will be assessed quantitatively and qualitatively. Fidelity to TEAM processes, content and format will be evaluated by random attendance of 20% of sessions by non-interventionist study staff to determine if sessions covered relevant TEAM constructs and health practices as identified in the specific sessions as well as assessment of if written prompts were appropriately utilized, and if sufficient time was devoted to the question/answer/ comment session. Each fidelity dimension will be rated on a 1-10 scale using the same evaluation process as in the TEAM pilot.

Risks to Research Participants
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 surveys 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 behavioral intervention intended to enhance self-management is not expected to increase risk to individuals. 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.

The risks to the participants will be primarily those of talking about some matters that they may find uncomfortable. All participants will have blood drawn twice, at baseline and at 6-month follow-up. There is minimal risk to blood draw. However, when a blood sample is taken, participants may experience temporary discomfort, bruising, and/or infection or blockage of the vein where the needle is put into their arm. On rare occasions, fainting may occur

PEDs are not expected to incur risk, however in the unlikely event that participation in TEAM is experienced as stressful, appropriate measures will be taken by the on-site clinical members of the study to minimize burden or distress.

Potential Benefit to Research Participants

While this research study is not developed to specifically benefit study participants, there may be several potential benefits to participants. Participants being interviewed may find it helpful to discuss their experience. Some participants may benefit from participation in the sessions (e.g., improved health, improved understanding of stroke risk factors, and understanding of the importance of and development of self-care behaviors).

There is no guarantee of benefit to any participant. However, it is the goal of this project to contribute knowledge, which can be useful in improving understanding and management stroke risk factors. It will be explained to participants that their involvement in the study may not benefit them in any way but may be of benefit to other patients in the future.

Provisions to Protect the Privacy Interests of Research Participants

Every effort will be made to protect the individuals' privacy. The study staff will make sure the questionnaires and assessments are done as privately as possible. Complete confidentiality cannot be assured due to the nature of group interactions. Participants in the TEAM intervention will be requested to maintain other participants' confidentiality. Confidentiality of research data will be protected in several ways. Patient identifiers at the analytic level will not be the same as the patient's clinical medical record number. Only aggregate data will be presented or published and will be presented such that individual patients cannot be identified.

All data collection will be done in Uganda. Makerere University, College of Health Sciences IT infrastructure is comprised of 6 servers and more than 200 computers/laptops and have developed a custom Data Management System that is used to manage the data, using SQL Server as the backend for all secure data storage. MS Access is used for double data entry and SAS programs are used for comparing 1st and 2nd entry and generating discrepancy reports. DTS/SSIS packages are used to automatically import/export any new data and stored procedures written in T-SQL are used to automatically generate new data queries on a daily basis. There is a web interface to the whole system written in ASP.NET to allow users to view the data, view reports, and even modify the data they are authorized to access. With regular backups and a full audit trail, the whole system is regulatory compliant (21 CFR Part 11). All data saved in a secure fashion and accessible only by those who work on the study at the Uganda sites. US study staff will not have access to the Uganda sites network.

The paper data will be kept in files under lock and key in well secured file cabinets in a lockable room. All paper files will be shredded following the 45 Code of Regulations (CFR) part 74.53, which requires awardees to retain records pertinent to an award for a period of three years from the date of submission of the final expenditure report.

The access rights to research data will be confined to only those who work on the study. Collected data containing confidential information will be stored in a secure locked room and only accessible to authorized individuals. Audio recordings and other data captured in the field will be uploaded to a secure, managed server at the earliest opportunity. This will ensure they are held securely and backed-up on a regular basis. Sessions will be audio recorded and transcribed by hand in to a Word document. Audio recorders will be will be stored in a secure locked room and only accessible to authorized individuals. The un-anonymised transcript will be stored in a secure location for the time period that it is needed. The transcripts will then be de-identified and uploaded to CWRU Box for analysis by the CWRU data team. The recorded information will be destroyed after transcription by deleting the voice files and reformatting the recorder. If an anonymised derivative has been produced and the raw transcript is unlikely to be re-used, the un-anonymised version will be destroyed upon grant closure. The anonymised transcript will be kept for 10 years, unless there are third party requirements that require it to be deleted. No software will be used to record or transcribe data.

Once the study is completed, de-identified data will be transferred to CWRU site, which will be done by the Uganda sites uploading the de-identified data from their secure serves to CWRU Box.

No software will be used to record or transcribe data.

RCT study data will be entered and saved in to CWRU REDCap.

Withdrawal of Research Participants
Participants are free to withdraw from the study at any time. There are no special procedures to follow if participants no longer wish to participate. The PIs may chose to stop participations for individuals if it is in the individuals' best interest.

Alternatives to Participation
The alternative is for research subjects not to participate.

Costs to Research Participants
There are no costs to research participants. All expenses, including blood draws are covered by the grant.

Research Participant Compensation
All RCT participants will be paid a modest amount to compensate for time and travel to research assessments. Participants will be reimbursed uShs 55,887 (approximately US$15) for each quantitative screening, baseline, and 13-week interview and uShs 74,516 (approximately US$20) for the final (6-month) interview and for each qualitative interview.

The patient study participants will not receive compensation for attendance at the TEAM or ETAU sessions, however they will receive modest compensation for the travel costs required to arrive/depart from the TEAM or ETAU session. Care partners/family members of patient participants will also receive modest compensation for the travel costs to arrive/depart form the TEAM or ETAU sessions. Health clinic staff will receive modest compensation for the time required to participate in a single focus group on TEAM process measures.

Peer educators will receive uShs 22,355 (approximately US$6) for each TEAM session and for each TEAM training session that they attend.

Provisions to Monitor the Data to Ensure the Safety of Research Participants
The study PIs, Drs. Katabira and Sajatovic, will monitor the study to ensure data integrity and the safety of the participants. The MakCHS site Data Coordinator, will review the data for discrepancies on a regular basis and will review the study records for compliance with IRB requirements and verification of source documents. Ugandan investigators and research staff will be responsible for all stages of the project: recruiting and consenting participants, conducting the surveys, qualitative interviews, and conducting all study assessments. They will be responsible for all data collection. Management of data will take place at MakCHS, but de-identified data will be transferred to CWRU for final analysis.

The data safety and monitoring plan for this project consists of several components, as outlined below. The PIs (Dr. Martha Sajatovic & Dr. Elly Katabira) will be responsible for ensuring that this plan is followed during the course of this study.

1. Approval from the Case Western Reserve University (CWRU) Institutional Review Board (IRB) and from the Makerere College of Health Sciences (MakCHS) 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.
2. Drs. Katabira & Sajatovic will conduct regular research staff meetings to closely monitor study start-up and progress, including oversight of staff training and research capacity building. As was done in the Neurology MEPI and in the R21 pilot study, meetings that involve both Ugandan and U.S. study team members will be held via web teleconference. Meeting minutes will be sent to research staff participants. More frequent local meetings and ad-hoc full team meetings that may be called in the event that problems or concerns arise during the study period will supplement the regularly scheduled web calls.
3. There will be at least 2 in-person visits to the sites annually by the U.S. PI.
4. **Adverse event identification/classification:** The study investigators and/or qualified research assistants will identify adverse events. All adverse events, whether considered serious or not, will be recorded and reviewed by the study PIs on an ongoing basis, and reported to the IRB according to local IRB policy. Serious adverse events are defined as events that result in any of the following: death; a life threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect (or an event that may require

medical or surgical intervention to prevent one of the outcomes listed above). Strokes will be recorded if/when they occur and will be considered serious adverse events. All adverse events, including all serious adverse events, will be reported to the IRB according to local IRB policy and to the Data Safety and Monitoring Board (DSMB). A summary report of all adverse events will be submitted to NINDS annually, and at the end of the study.

5. **Data and Safety Monitoring Board (DSMB) and safety review plan:** We recognize the need for careful, expert external data and safety oversight to ensure the wellbeing of the participants in this study and the scientific integrity of the project. These experts, who are not members of the study team, will review and evaluate the accumulated data for participant safety, adverse events, study conduct and progress, at minimum, every 12 months. Ad-hoc meetings might be called to evaluate unanticipated serious adverse events or any other urgent issues that are relevant and which might occur during the course of the study. The DSMB will be comprised of two clinicians with stroke expertise at the Uganda site; a faculty member/clinician with stroke expertise at the US site, and a biostatistician at the US site who are all not part of the study team, but have extensive experience with federally funded research. The DSMB communication and oversight will be accomplished via telephone, SKYPE, or email communication for issues that need more immediate attention.

The PIs will review study progress and safety regularly as described above. As noted above, progress reports, including patient recruitment, retention/attrition, and adverse events will be provided to the DSMB at least annually for independent review. The annual report will include a list and summarization of adverse events. In addition, the annual report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. There will be an interim analysis conducted once half of all trial participants have completed the 6-month outcome evaluation point. The annual report will be signed by the PI/designate and will be forwarded to the DSMB. The DSMB will review the annual plan on all 5 points outlined above, as well as the interim analysis, and make recommendations to the appropriate regulatory agencies (IRB, NIH) concerning continuation, modification or termination of the study. The PI will provide a copy of all DSMB reports to the appropriate IRB and NIH on an annual basis.

Data Analysis Plan

Quantitative data Analysis: Preliminary descriptive analyses will examine change over time in systolic BP as well as secondary outcomes. The measures of interest are valid and reliable, and have been used in stroke studies in the SSA setting.[24, 30, 88, 97, 98] Primary and secondary outcome measurements will be assessed at baseline prior to randomization to either TEAM or ETAU, and at the 13 week and 6 month time-points using the same methods as in our pilot work. Of primary interest is the treatment by time interaction in systolic BP, measured from baseline to 6 months after randomization between TEAM and ETAU. Explanatory variables will include age, gender, stroke history and rural vs. urban status.

The 13-week systolic BP measurement will reflect the period following baseline (when individuals participating in TEAM Uganda will have just completed the “intensive” group sessions), and it will be used to assess for within-subject differences from baseline to 13 weeks and 13 week to 6-month time periods. This will allow for a greater understanding of the time course for when the expected reductions occur in the TEAM Uganda group, which we expect to mostly occur after the “intensive’ group sessions have ended. We will analyze change from baseline to 13 weeks as well, analyzing contrasts within the mixed model framework.

For aim 2, we will use 2 group by 3 time waves repeated measures analysis of variance (RMANOVA) for each of the 3 hypotheses in Aims 2. These analyses will compare two groups (TEAM intervention vs. enhanced treatment as usual (ETAU)) across three time waves of systolic BP (H1), serum cholesterol (H2), and serum HbA1c (H3). When using a repeated measures ANOVA, it not only assesses mean differences across time, but also assesses group differences, as well as, the interaction of time X group which will allow us to test the trend of the means over time across the three groups. The repeated measures ANOVA, not only can be used to determine if there are mean differences across the three time periods, it can also utilize orthogonal polynomial contrasts to determine linear and quadratic trends of the means across time. Orthogonal polynomials are weights

assigned to each time period that model a linear or quadratic (non-linear) trend. Repeated measures ANOVA can determine if these trends in the means are significant. A linear trend is indicated if there is a steady increase or decline in scores from the first time wave to the third time wave. A quadratic trend is indicated if there is a change in direction based on scores across the time waves. For example, if there is a decrease in mean scores from T1 (baseline) to T2 (13 weeks), but an increase in scores at the T3 (6 months), this would be indicative of a U trend for the three time periods and a return toward the mean score from T1 to T3. A quadratic trend can also indicate a single change in direction in the trend of the means, for example, if there is a decline in means scores from T1 to T2, and the decreased mean score is maintained at T3. The major assumption to be tested with repeated measures ANOVA is sphericity. Sphericity is a form of compound symmetry and refers to the equality of variances of the differences between each time wave. [99] If the assumption of sphericity is violated based on the Mauchly's test, SPSS provides an adjusted F, df, and p-value in repeated measures ANOVA to account for this violation. We may also explore repeated measures mixed model approaches to analyze change from baseline to 13 weeks as well, analyzing contrasts within the mixed model framework.

Secondary outcomes: We will model secondary outcomes over time in a similar manner. We will consider generalized linear models when distributions of outcomes are not approximately normally distributed, or transformations of outcome variables to normality. We will also conduct exploratory moderator analyses of the explanatory variables in the primary mixed model. Mediation analyses also will be explored. Potential mediators include dose of TEAM session exposure, medication prescription/access and adherence to a heart healthy diet. Variables with (change) values that appear to be associated with change in systolic BP levels and that appear to differ by treatment will be considered further as mediator variables, following as in MacKinnon (2008)[100] and Preacher and Hayes (2008).[101] This will involve single mediator analyses as well as multiple mediator models. These analyses will involve the treatment variable and change in systolic BP values. Associated standard errors of estimated indirect effects will be derived through bootstrapping, using the M-Plus software.

Sample size calculations: From our pilot data, mean baseline systolic BP was 162.9 (SD 25.6). Change from baseline to 6 months with the TEAM Uganda intervention saw a mean systolic BP of 149.7 (SD 22.1). Reductions BP of ≥2 mm Hg can significantly reduce the incidence of cardiovascular disease and it's complications in both hypertensive and normotensive individuals, and reductions of the magnitude seen in this team's pilot work is well above thresholds that are considered clinically meaningful.[94, 95] Our projected sample size is n=246, with 123 participants per arm. Based on our preliminary mixed model, we observed difference in systolic BP from baseline to 24 weeks of 13.22, with standard deviation of 25.84, and within subject correlation parameter value of 0.57. However, we will conservatively estimate our sample size based upon a difference of 10 mmHg, commensurate with a meta-analysis that used this magnitude of change in BP across a large sample with varying baseline blood pressure levels and comorbidities.[96] Also in our pilot work with the TEAM Uganda study, we observed an attrition rate of 12.5% at 6-months follow-up. Conservatively, for this study, we will assume 25% attrition. Finally, to assume for two-sided test of time-by-treatment group interaction, Type I error level is 0.05. Then, in a linear mixed model with subject-level and center-level random effects, power is 0.80 for a clinically significant difference of 10.0 mm Hg between treatment arms for the projected sample size of 246 subjects in total. We should thus have sufficient power. We do assume compound symmetry over the 3 time periods. We will also consider an AR(1) covariance model, and compare model fits.

Missing Data: Strategies to minimize loss to follow-up are outlined in Form E, specifically the description of our Recruitment and Retention Plan. Data that remain missing despite our retention efforts will be accommodated in our analyses and their impact evaluated through sensitivity analyses. The models we propose can be estimated without bias under the missing at random (MAR) assumption[102] and provide valid analysis as long as covariates associated with missingness (if any) are included in the mixed model. To assess which covariates may be associated with missing outcome data, we will create binary indicators of whether the outcome was missing (=1) or not (=0). If a covariate is correlated with missingness at r >0.40 and is correlated at r >0.40 with the original response variable, it will be included in the analysis as an auxiliary correlate.[103] We will conduct assessment of the missing at random (MAR) assumption by pattern mixture models that relax the missing at random assumption, while analyzing the sensitivity of treatment by time interaction effects. . We will also consider using Full Information Maximum Likelihood models in presence of incomplete data. [104]

Qualitative data analysis plan: PIs at each of the proposed study sites will be responsible for overseeing data input and quality

Two qualitative researchers will be used to ensure standardization of qualitative analysis. 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"*[105] or relevant *"themes and categories".*[106] Each researcher will further read/code each document independently and iteratively until no new insights emerge. Initial codes will be recorded using *NVivo.* 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.[106, 107] Although code definitions are mutually exclusive, the same portions of text can be attached to multiple codes. The refined codes will then be applied to the transcripts, with coding decisions recorded electronically using *NVivo.* All transcripts will be coded by both qualitative researchers. In our previous research, checks for inter-rater consistency using Cohen's Kappa [108] yielded Kappa ≥ .90 which was considered excellent agreement.

NVivo will be used to retrieve all segments of text attached to a particular code to create code-based files across all respondents. The qualitative team will further elaborate, refine, and differentiate the codes and identify similarities and differences through comparison of respondents. Emergent observations will be recorded in theoretical memos using *NVivo's* Project Document feature. This process of engagement with the data and iterative discussions will be repeated until all discrepancies are resolved and no new insights emerge.

Table 1: RCT Schedule of study events

PROCEDURES	Screen	Baseline	Wk 1-12	Wk 13	Wk 13 - Mth 6	Mth 6	Mth 12
Identification of participants: Inclusion/Exclusion criteria review	X						
Informed Consent	X						
Demographics	X						
Medical Status & Burden: Self-reported Charlson Comorbidity Index Medications Personal and family stroke history		X					
Randomization		X					
Primary Outcome: Systolic BP		X		X		X	
Secondary Outcomes: Diastolic BP Serum cholesterol HbA1c Serum HDL, LDL, triglycerides BMI Diet questionnaire GPAQ GATS AUDIT General self-efficacy Stroke knowledge INTERSTROKE stress Medication adherence (MARS)		X		X		X	

Medication Access Health resource use							
Qualitative Assessment Patient Clinicians/Administrators SAB**		X		X X*			
Intervention attendance			X				
Enduring effects of the intervention							X

*** Clinicians who refer patients will be assessed when their patient reaches the 6-month time-point. A sample of clinician/ administrators will be assessed in Year 4 to assess overall value/alignment of the intervention.**

**** The SAB will be assessed in Year 5.**

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