Protocol Title: **MAMBO: Measuring Post-Stroke Cognitive, Ambulation, Motor, and Behavioral Outcomes in Tanzania**
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Funding: National Institutes of Health (R21)
Version date: 11/30/2020
Version 4.3

I. Background and Significance:

There is an under-recognized and growing epidemic of stroke in sub-Sharan Africa. Stroke is the leading cause of death and disability globally and accounts for more deaths than HIV/AIDS, malaria, and tuberculosis combined.[1,2] Sixteen million people suffer a first-ever stroke each year worldwide. Of these, 5.7 million die and 5 million survivors remain disabled. In the United States, a person suffers a stroke every 40 seconds and dies of stroke every 4 minutes. In low- and middle-income countries (LMIC), the incidence of stroke is even higher: 85% of all strokes occur in LMIC.[3,4,5] There exists research on post-stroke cognitive outcomes; however, little research has specifically centered LMIC populations that may benefit from the implications of such work.

Additionally, this study has been funded by the NIH's Fogarty International Center. The funding opportunity is on global brain and nervous system disorders research with a requirement to have a foreign site that is a low- or middle-income country. The funding mechanism is meant to build capacity and enhance the understanding of brain disorders in the world's low- and middle-income countries in collaboration with a high-income country. This study site is in the United Republic of Tanzania, a low-income country according to the World Bank (2016) designation. The Massachusetts General Hospital in the U.S.A. is the high-income country which will participate in capacity building and support all research endeavors. Ipso factor the study will be in a low-income country and in this case, in Tanzania, due to its synergies of need, science, and human resources.

There are multiple possible benefits to the participants of this study, including accessibility to more expertise, increased access to physicians, and expert-provided care. In several cases, participants may receive better than usual care while enrolled in the study. Some may go on to receive neurosurgical intervention or have a diagnosis that is treatable (e.g. diagnosis of liver disease).

A more thorough appreciation of stroke and its etiologies is likely both to lead to better clinical care and to inform new directions for care at MNH. Participants will receive free head CT imaging to potentially identify unrecognized and untreated causes of stroke. This could lead to improved health knowledge and more selected treatment approaches and care.

At MNH, training and knowledge of stroke, clinical research, and neuroimaging will occur throughout this study. Neurological research and focused expert neurological care post-stroke are nearly non-existent in Tanzania. Therefore, initial care provisions for brain disorders will provide foundational knowledge of neurological care to health care workers. This is likely to lead to better medical care for future patients with stroke who are not involved in the study.

II. Specific Aims:

(1) To calculate the cognitive outcomes, as measured by the SIDSA and MoCA for 90 days post-stroke in 200 participants. (2) To collect medical history survey data from 200 participants. (3) To calculate other variables of interest to the study population, including motor recovery (FugI Meyer, modified Rankin scale), depression (PHQ-9, Asberg Depression Scale), lab variables (serum sodium, ALT), and quality of life (Stroke Impact Scale).

III. **Subject selection:**

Both male and female subjects greater than 18 years old and subjects from any racial and ethnic group may be enrolled in the study. Tanzania is an ethnically homogenous country; nearly all residents are ethnically Tanzanian. Therefore, in practice we expect little to no enrollment of other ethnicities and races beyond Tanzanian Africans. Recruitment of an approximately 1:1 male to female ratio is expected. Total recruitment is aimed at 200 participants with new-onset acute ischemic or hemorrhagic stroke presenting at Muhimbili National Hospital (MNH) within 21 days of symptomatic onset.

No children will be enrolled in the study. The mechanisms of stroke in pediatric age groups are presumed to be very different (e.g. non- atherosclerotic) and are outside the scope of the study question.

Study recruitment will occur exclusively at Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania. Patients presenting to the hospital with symptoms of stroke will be administered a head CT paid for through study funds. The head CT will thus be administered as part of the screening process, not the study itself. Head CT is, in principle, the standard of care at MNH for patients with stroke; however, in reality most patients cannot afford a head CT within 21 days of presentation. Many patients do, at some point, receive a head CT, but it generally takes time as the patient's family members must come together to pool financial resources to pay for the scan. In the interest of financially equitable subject selection – in order not to immediately screen out poor stroke patients who cannot afford head CT – we have made the decision to pay for head CTs for all patients who present with the symptoms of stroke. The head CT will be read by a local team, which will determine ischemic or hemorrhagic stroke. A consulting neuro-radiologist will confirm the local team's findings.

Sub-classification of ischemic or hemorrhagic stroke will be based on the TOAST (1993) categorization. Following confirmation of ischemic or hemorrhagic stroke, study investigators will determine patient eligibility for inclusion in the study. The investigators will administer questionnaires to collect patient health history and perform blood tests to measure physical health characteristics. Questionnaires will follow the Get with the Guidelines® survey intake forms of the American Heart Association, as developed in preliminary studies. Blood tests will be comprehensive: Testing for HIV will include CD4 count and viral load (HIV ELISA and Uni-GoldTM) performed at MNH; serum sodium, potassium, liver tests, creatinine, and hemoglobin A1c will be tested; women of childbearing potential will have a B-HCG test. Participants will be screened for dysphagia. Sub-classification of ischemic stroke will be based on the TOAST (1993) categorization.

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Participants will be screened by study physicians upon presentation for eligibility according to the following exclusion criteria: (1) NIH Stroke Scale Score >20 points, (2) unconscious at presentation, (3) transient ischemic symptoms <24h, (4) history of recent head trauma, (5) baseline motor deficits from other etiologies including prior stroke, and (6) patients who are moribund for other reasons and unlikely to survive to 90 days will also be excluded from participation. Additionally, (7) contraindication to MRI (e.g. piercings/tattoos, electronic/metallic implants, claustrophobia). All assessments of exclusion criteria/safety will be conducted by trained, IRB-approved study neurologists who are familiar with the procedures.

If a patient is found eligible, he or she will be approached, in person, by Tanzanian study coordinators and presented with the opportunity to enroll in the study.

IV. **Subject Enrollment:**

Consent will be obtained after confirmation both of acute ischemic or hemorrhagic stroke and patient eligibility criteria. A trained study staff member who is a licensed physician, without prior clinical connection to the patient, will be present in person to administer consent forms either in Swahili or English. Since there is limited outpatient stroke care prior to a new-onset stroke, we do not anticipate familiarity between the neurologist on duty at MNH and the newly admitted patients.

Since 50% of strokes occur in the dominant hemisphere and 50% of strokes occur in the non-dominant hemisphere, we expect that about half of eligible patients will be unable to give independent consent for participation. This is because strokes that occur in the dominant brain hemisphere can result in aphasia, dysphasia, or motor deficits in the dominant hand. There is no ethical or legal prerogative to exclude 50% of stroke patients simply because they are unable to speak or move their hand. Thus, in the case that study investigators encounter aphasic, dysphasic, or motor-impaired patients, investigators will seek surrogate consent through a medical proxy.

Additionally, stroke patients often experience fluctuating states of lucidity, which can result in various decisional or cognitive impairments. Surrogate consent will be sought from medical proxies in the case of patients with decisional impairments. Such patients should be included in research to study interventions that can potentially benefit their condition and their recovery. Furthermore, inclusion of patients with decisional impairments is currently standard in stroke research.

Three classes of medical proxies will be allowed to give surrogate consent in writing. These classes are, in preferred order: (1) a court appointed guardian with specific authority to consent to participation in research studies or the authority to make health care decisions within the class of diagnostic and therapeutic procedures of this study. (2) A proxy with durable power of attorney with the specific authority to make health care decisions inclusive of this research. And (3) a spouse, adult child, or other close family member who knows the potential participant well and has been previously involved in their care or any other class of surrogates that the local ethics committee deems appropriate. A surrogate who provides consent will be advised that his/her decision should reflect the potential participant's own views when he/she had the capacity to express them. If the potential subject did not previously express a view on the matter, the surrogate will be advised to make a decision based on the potential subject's best interest.

If a medical proxy is necessary to provide consent for a subject's participation, a note will be made in the research record. The relation of the proxy to the subject will be recorded as will the subject's ability to provide assent to participation. If the subject provides assent, this will be noted. If the subject is unable to provide assent due to his/her medical condition, a note documenting this will be made in the research record.

Participants will be enrolled if they meet eligibility criteria (> 18 years of age, confirmed ischemic or hemorrhagic stroke), are able to provide written consent or have a medical proxy who can provide surrogate consent, are able to be contacted for follow up at 30, 60, and 90 days, and are willing to be examined and interviewed by study investigators on the outcomes. Participants must be geographically reachable and able to either return to MNH or have a study investigator complete a home visit at 90 days. Participants >100km away by land or residing on islands will be considered geographically unreachable.

Tanzanian investigators will be primarily performing screening, consent, and enrollment. Participants will be asked for contact information including phone number and address. Three additional ways to contact the participant will be inquired including phone numbers of next of kin.

Following the consenting process, Tanzanian site investigators will provide participants with a study ID number.

V. Study Procedures:

After consent has been furnished, study staff will record baseline data for each subject. The majority of baseline data will come from the screening process, including serum sodium and hepatic enzyme levels. They will receive an MRI brain. Initial motor impairment will be evaluated through the Fugl-Meyer Motor Scale, the assessment of which will be digitally filmed in order to allow for validation of aberrant scores. Recordings of the Fugl-Meyer assessment will be stored on encrypted, password-protected external hard-drives. Participants in the videos will be identified only through study ID number and the files will be labeled with the study ID number. The video will be used to validate Fugl-Meyer scores; since the Fugl-Meyer assessment is complex, if any issues arise in the administration and scoring

process, we will be able to show the video to study-staff who are experts in the Fugl-Meyer assessment to guarantee that each subject's baseline Fugl-Meyer score is accurate. Participants will have initial cognitive capacity measured through the MoCA scale and IDEA scale, administered in English or Kiswahili per patient preference.

Study participants will be contacted within three days of the 30-, 60-, and 90-day time-points to schedule an in-person visit, either at the hospital or at the participant's home. At each study visit, participants will be evaluated for medication and evaluated for adverse side-effects through verbal inquiry on the part of the investigator; investigators will draw 10-15mL of blood, in order to perform sodium and hepatic enzyme labs; investigators will assess participant disability through the modified Rankin Scale (mRS).

Analysis of serum sodium and hepatic enzyme levels will be conducted at MNH. Blood samples will also be shipped to the US for analysis of biomarkers of post-stroke cognitive decline.

If participants are unable to be reached in person during the 30- and 60-day follow-up visits, they will be called by Tanzanian site investigators. During these calls, investigators will evaluate the mRS of the participant and will inquire about adverse side-effects. The 90-day follow-up will occur either at MNH or at participants' home, whichever location was indicated as preferable during the screening and consent process.

Study Design: This study will be an observational trial to determine cognitive outcomes for 90 days following acute ischemic/hemorrhagic stroke in Tanzania. 200 patients presenting to Muhimbili National Hospital (MNH) with acute stroke will be enrolled. Subjects will be followed at 30, 60, and 90 days. The study endpoint will be considered as completion of the 90-day follow-up. Subjects will be remunerated the Tanzanian Schilling equivalent of 50 USD.

Objectives: (1) To calculate the cognitive outcomes, as measured by the SIDSA and MoCA for 90 days post-stroke in 200 participants. (2) To collect medical history survey data from 200 participants. (3) To calculate other variables of interest to the study population, including motor recovery (FugI Meyer, modified Rankin scale), depression (PHQ-9, Asberg Depression Scale), lab variables (serum sodium, ALT), and quality of life (Stroke Impact Scale).

All 90-day assessments will be administered by senior site investigators, who will also take the final 10-15mL blood draw, evaluate participant mRS, and inquire about adverse events. Participants will receive a second MRI brain at 90-days and will be administered the MoCA and IDEA screens. As at baseline, the 90-day Fugl-Meyer assessment will be filmed and stored on an encrypted external hard drive. In the case of aberrant scores or difficulty scoring, the video will be shown to expert study staff for validation of the correct Fugl-Meyer score.

It is possible that during the 90-day raft of questionnaires, participants will endorse survey questions that indicate suicidality. In such cases, participants will be formally referred to the study-site neurologist for psychiatric care and thorough psychological evaluation. Participants

will be referred to the managing neurologist because the number of psychiatrists in Dar Es Salaam is very low.

It may be necessary to drop certain participants from the study. In such cases, Tanzanian site investigators will evaluate the participant's continued participation in the study according to the following drop criteria: (1) participants who develop a serious, non-stroke related disease, like cancer, that will alter their life or seriously affect their medicine regimen; (2) participants who die; (3) participants who are lost to follow-up, defined as not being available during three attempts at contact 3 days apart over the course of 9 days; (4) participants who are unconscious or bed-ridden, defined as having an mRS score of 5 or great; and (5) participants who become pregnant.

If a participant meets any drop criteria, Tanzanian site investigators will send a proposal, in writing, to U.S. site investigators to withdraw the participant from the study. U.S. site investigators will respond within 24 hours. When approved by U.S. site investigators, the participant will be formally withdrawn from the study. In cases where a participant develops a serious non-stroke related disease, he or she will be referred to appropriate physicians at MNH. In cases of death, loss to follow-up, or unconsciousness, Tanzanian site investigators will make a reasonable attempt to discover the circumstances surrounding participant withdrawal. Participant withdrawal will be noted in a Withdrawal Log alongside a brief explanation.

Payment will be provided to participants. Payment will be the equivalent of 50 USD, approximately 116,000 Tanzanian Shillings. We expect this amount to fully cover the costs of transportation to and from the MNH.

VI. Biostatistical Analysis:

Data will include stroke motor-function recovery, cognition, serum sodium and hepatic enzyme laboratories, and quality-of-life/depression data, which will be captured, respectively, through changes in the Fugl-Meyer motor assessment between study enrollment and completion, through the IDEA and MoCA assessments, and through both the Asberg Depressive Symptom and PHQ-9 questionnaires.

The number of participants has been chosen based on an estimated natural history from our pilot observation work. A post-stroke mortality of approximately 30% at 90 days is assumed. Of n=200 enrolled participants, 140 are assumed to be alive at 90 days.

VII. Risks and Discomforts:

Risks associated with blood draws: During venous blood draws the skin is pierced by a needle. Any insult to the skin can result in discomfort, pain, and bruising. There is a slight risk of infections associated with blood draws. Risks will be minimized through the use of established blood-draw safety protocols, including exclusive use of sterile needles and use of alcohol swabs to disinfect the skin area that the needle will pierce.

Risks associated with MRI: During MRI, patients can experience discomfort due to the loud noises and closely enclosed space of the machine. Risks will be minimized by explaining MRI procedures to patients. MRI is also known to be safe and used in routine stroke clinical care in the US.

Potential psychological stress/discomfort: There exists a risk of incurring psychological discomfort due to diagnostic questions about mood. Discomfort includes embarrassment, anxiety, panic, or depression. In the event of severe psychological distress, subjects will be promptly referred to appropriate mental health experts.

Potential risks due to higher than usual standard of care: Participants in this study will be exposed to a better than normal standard of care. This includes access to physical and neuroimaging exams that may normally be outside patients' financial reach. There is a risk of identifying a previously unknown serious medical illness or subclinical finding on brain imaging. Such a finding could cause a participant to be worried, anxious, or scared; however, discovery of an unknown, potentially life-threatening condition will prompt immediate care. The care that patients then receive will be at least as good as usual care, if not significantly better due to institution of systematized evaluations, documentation, free neuroimaging and blood tests, documentation of clinical course, and access to a team of expert physicians throughout the course of the study.

Potential risks related to data safety and security: Participants will be exposed to risk of loss of confidentiality and breach of privacy. Such risks are related to the collection and maintenance of study data, the collection of video recordings of study procedures, and the collection of blood samples. These risks will be protected against via secure software purchases, secure data storage, training of study subjects in confidentiality best practices, and disclosure to participants of the intent to maintain data security at all times. All files of recordings of Fugl-Meyer assessments will be labeled only through participant ID.

Unanticipated problems involving or giving rise to risks to subjects, including adverse events, will be reported to the Partners Healthcare Research Council (PHRC) in accordance with PHRC unanticipated problems reporting guidelines.

VIII. **Potential Benefits:**

There are multiple benefits to the participants of this study, including accessibility to more expertise, efficiencies in the MNH healthcare system, access to physicians, and expert-provided care. In several cases, participants may be better treated and their underlying conditions better addressed. Some may go on to receive neurosurgical intervention or have a diagnosis that is treatable (e.g. diagnosis of liver disease).

A more thorough appreciation of stroke and its etiologies is likely to lead to better than usual clinical care and inform new directions for care at MNH. Potential participants will receive free head CT and MRI imaging- better than usual care- to identify unrecognized and untreated causes of stroke. This could lead to improved health knowledge and more selected treatment approaches and care.

Among the health care Hospitals, training and knowledge of stroke, clinical research, and neuroimaging will occur throughout this study. Neurological research and focused expert neurological care post-stroke are nearly non-existent in Tanzania. Therefore, initial care provisions for brain disorders will provide foundational knowledge of neurological care to health care workers. This is likely to lead to better medical care for future patients with stroke who are not involved in the study

IX. **Monitoring and quality assurance:**

All adverse events, both those considered serious and those considered non-serious, will be recorded in an adverse events log; however, serious adverse events (SAE) will prompt swift action to preserve patient safety. Serious adverse events are defined as: death, a life-threatening event, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant physical disability/incapacity, and/or congenital anomalies or birth defects. Non-serious adverse events include stomach discomfort and gastrointestinal distress.

All serious adverse events/experiences as defined will be reported to the project manager at MNH and then to MGH within 24 hours of the Tanzanian site's awareness, regardless of whether the Tanzanian investigator feels that the experience is related to the study or was expected. Within that 24-hour period, the site investigator in Tanzania will also complete a MedWatch FDA form 3500 (or modified version of this for the Tanzanian authorities) and email it the MGH site. For AE or significant abnormal results that are identified during a visit, telephone call, or other study activity, the site staff will ensure that the information is available to the participant and his/her primary physician (should one exist). The number of patients with primary physicians in Tanzania is very low. As appropriate and permitted by the participant, the primary care physician will be notified by the research staff via written correspondence to ensure follow up. If the finding affects the participant's immediate safety (e.g. laboratory value far out of range), appropriate and immediate action will be taken by the site investigator to ensure the participant's wellbeing.

The site study staff will assess AEs at every point of contact with subjects by recording all voluntary complaints by the participant and by assessment of clinical features. All AEs will be recorded in a study Adverse Events log. The log will include the event term, onset date, resolution date, AE, and participation in the study. If a participant is withdrawn from the study, it will be recorded. Causality definitions will include the following: unrelated (no possible causation), unlikely (not reasonably related although a causal relationship cannot be ruled out), possibly (causal relationship uncertain), probably (high degree of certainty for a causal relationship), and definite (causal relationship certain).

Additionally, participants will be advised in the written consent form that they have the right to permanently discontinue the study medication and/or withdraw from the study at any time without prejudice and may be withdrawn from the study at the discretion of the Tanzanian site investigator or MGH principal investigator. Administrative reasons for participant withdrawal include: participant withdrawal of consent, request of investigator or PI, request of primary care physician, nonadherence to study procedures, protocol deviation, and premature termination of the study.

Patient safety will further be ensured through the appointment of an independent data safety monitoring board (DSMB). The responsibilities of the DSMB will span review of the research protocol and ongoing study activities, review of the adequacy of participant recruitment and retention, data quality and completeness, and fidelity to the research study protocol. On a regular basis, the DSMB will review medical data connected to the trial; it will track SAEs, medical discontinuations, and premature withdrawals in real time. The frequency and format of DSMB meetings and reports will be established prior to study participant enrollment. Its scope and operations are specified by the "NINDS Guidelines for Data and Safety Monitoring in Clinical Trials" at http://www/ninds/nih/gov/research/clinical_research/policiies/data_safety_monitoring.htm. If

there is a significantly greater than expected occurrence in the incidence of SAEs, the DSMB will make recommendations to the study PI concerning trial continuation, modification, or termination.

X. References:

1 GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877-97.

2 Walker RW, Viney R, Green L, et al. Trends in stroke admissions to a Tanzanian hospital over four decades: a retrospective audit. Trop Med Int Health 2015;20:1290-6.

3 Stenumgård PS, Rakotondranaivo MJ, Sletvold O, et al. Stroke in a resource-constrained hospital in Madagascar. BMC Res Notes 2017;10:307.

4 Walker RW, Viney R, Green L, et al. Trends in stroke admissions to a Tanzanian hospital over four decades: a retrospective audit. Trop Med Int Health 2015;20:1290-6.

5 Seremwe F, Kaseke F, Chikwanha TM, Chikwasha V. Factors associated with hospital arrival time after the onset of stroke symptoms: A cross-sectional study at two teaching hospitals in Harare, Zimbabwe. Malawi Med J 2017;29: 171-6.

6 GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877-97.

7 Baatiema L, Chan CKY, Sav A, Somerset S. Interventions for acute stroke management in Africa: a systematic review of the evidence. Syst Rev 2017;6:213.

8 Stenumgård PS, Rakotondranaivo MJ, Sletvold O, et al. Stroke in a resource-constrained hospital in Madagascar. BMC Res Notes 2017;10:307.

9 Okeng'o K, Chillo P, Gray WK, et al. 3Early mortality and associated factors among patients with stroke admitted to a large teaching hospital in Tanzania. J Stroke Cerebrovasc Dis 2017;26:871-8.

10 Walker RW, Viney R, Green L, et al. Trends in stroke admissions to a Tanzanian hospital over four decades: a retrospective audit. Trop Med Int Health 2015;20:1290-6.

11 Ezejimofor MC, Uthman OA, Maduka O, et al. Stroke survivors in Nigeria: A door-to-door prevalence survey from the Niger Delta region. J Neurol Sci 2017;372:262-9.

12 Mead G, Hackett ML, Lundstrom E, et. al. The FOCUS, AFFINITY, and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicenter randomized controlled trials. Trials 16:369 (2015)

13 Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scandinavian journal of rehabilitation medicine. 1975;7(1):13-31..

14 Inc, P. Pillsy | 24x7 Digital Medication Coach, with smart pill bottle and app. Available at: https://www.pillsy.com. (Accessed: 3rd October 2018)

15 Kroenke, K., Spitzer, R. L. & Williams, J. B. W. The PHQ-9. J Gen Intern Med 16, 606–613 (2001).

16 Montgomery, S. A. & Asberg, M. A new depression scale designed to be sensitive to change. Br J Psychiatry 134, 382–389 (1979).

17 Mead G, Hackett ML, Lundstrom E, et. al. The FOCUS, AFFINITY, and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicenter randomized controlled trials. Trials 16:369 (2015)

18 Health, C. for D. and R. Medical X-ray Imaging - What are the Radiation Risks from CT? Available at: https://www.fda.gov/radiation-emittingproducts/radiationemittingproductsandprocedures/medicalimaging/medicalx-rays/ucm115329.htm. (Accessed: 3rd October 2018)