SYSTEMATIC INVESTIGATION OF BLACKS WITH STROKE- GENOMICS (SIBS-GENOMICS) STUDY

SEPTEMBER 5TH, 2022

PILOT TRIAL

Specific Aim. To determine the effectiveness of the Afrocentric stroke riskometer mobile phone application combined with the motivation stroke educational video and educational modules for improvement of individual awareness and reduction of the total quantitative risk of stroke through a randomized controlled trial among stroke-free adults in Nigeria and Ghana**.**

Study design: A feasibility pilot study involving stroke-free adults with at least 2 vascular risk factors for stroke assigned to an educational intervention for 2 months comprising of a stroke video and riskometer App aimed at improving stroke risk factor awareness and health seeking behavioural modification to control vascular risk (n=50) compared with a control group (n=50) who are offered one time counselling.

Study Sites: 3 sites across Nigeria and Ghana

Study Participants: Study participants will be CONSECUTIVELY selected from the existing pool of stroke-free controls in SIREN and SIBS Genomics studies across the 3 study sites (60 from Ibadan, 20 from Kumasi and 20 from Zaria). The vascular risk factor profile of these control participants has already been assessed. Stroke free status at enrollment will be reconfirmed using the locally validated version of the QVSFS.

Eligibility criteria: **Inclusion criteria**: (i) male or female (sex is a biologic variable of interest), (ii) age ≥ 18 years, (iii) with at least 2 stroke risk factors based on the list of 11 topmost modifiable risk factors identified in the SIREN study (including hypertension**,** diabetes mellitus, dyslipidemia, smoking, overweight, physical inactivity, or unbalanced/poor diet). (iv) ownership or access to smartphone in consenting stroke-free adults. **Exclusion criteria:** prior history of vascular disease (e.g., stroke, transient ischemic attack, angina, myocardial infarction, peripheral vascular disease, and atrial fibrillation), or cognitive impairment; not comfortable reading and writing, depression or other psychiatric disorders (through personal declaration) likely to affect the interventions; participation in another RCT; other conditions rendering the individual unsuitable to participate in this research as judged by treating physicians,

Justification for Eligibility Criteria: Individuals with existing high modifiable risk are more likely to be motivated to engage in behavioral change activities more so than those without.

Recruitment: Research coordinators (RCs) will obtain informed consent, schedule baseline assessment & alert statistician of a new participant to be randomized via REDCap. Randomization will be performed within 24 hours & baseline assessments within one week at the respective SIREN facility/community. Baseline assessment will include screening of all participants for stroke risk factors by trained RCs. Risk factor screening will include measurement of blood pressure, blood glucose and lipid profile, psychosocial assessment for stress, dietary recall to assess salt intake and vegetable consumption, waist circumference and body mass index.

Intervention: The app will not be installed on the smartphones during the pilot study to limit potential future exposure contamination. RCs will complete baseline screening assessment with participants and capture a screenshot of the individual's current global stroke risk score as a percentage, which will then be given to the participant via their smartphone (i.e., **screenshot of the score produced by the app**). Participants will be shown their risk scores and the specific risk factors identified through the screening. They will be asked to visit their doctors /primary care clinicians to facilitate management their risk factors through therapeutic lifestyle changes or pharmacotherapy, for example antihypertensives for hypertension, statins for dyslipidemia, or oral hypoglycemics for diabetes. This will be part of health seeking behaviour the app should promote, which will be assessed as part of process measure. Participants will receive monthly reminders on compliance/adherence to any clinician prescribed treatment or lifestyle modifications, as applicable, and to follow-up with primary provider if they haven't already and especially if their risks include hypertension, diabetes, or dyslipidemia. Participants will be asked to show their current global stroke risk to their clinician/doctor. As part of process measure, we will assess clinician acceptability and readiness to use the app to monitor their patients overall progress with total risk factor control. The records will be stored on our server, such that if they lose the score risk, the RC will be able to provide another copy (paper or digital) so their clinicians will still be able to access risk scores when shown by participants. In

addition, participants will be encouraged to watch the stroke video at least once monthly that will be shared via their smartphone, although they will be asked not to share it with others to minimize exposure beyond enrolled intervention participants.

Control group will be screened at baseline and be informed about their risk factors. They will be encouraged to seek medical therapy for a doctor after assessment of their baseline risk factors, should they have hypertension, diabetes, or dyslipidemia, but this advice will not be reinforced by either exposed to the app or the stroke video. They will complete a post-study questionnaire to assess any contamination with the intervention.

Randomization: will be at individual level, per site as the app is meant to be developed at individual level eventually.

Concealment of allocation: Blinding of participants is not possible given the nature of the intervention. However, the adjudicator and the study statistician will not be aware of the allocation status of study participants during outcome data collection and analysis respectively. Outcome assessors will not be involved in delivering the intervention. To ensure blindness, trial participants will be told not to divulge details of their treatment to the assessors. The randomization scheme which will be used to allocate patients to groups will be developed & maintained by the lead study biostatistician. Randomization database will be independent & will not be accessible to outcome assessors or other personnel. Whereas the research coordinators (RCs) will be aware of the randomization assignment, they will not have any role in the delivery of the intervention or outcome adjudication.

Outcome measures:

1. **Feasibility measures**: Proportion approached, proportion refused, proportion ineligible (reasons for ineligibility), proportion enrolled, proportion completing follow-up, & proportion visiting their doctors will be compared between the two groups.
2. **Satisfaction and acceptability measures**: (i) autonomous self-regulation was assessed using the 15-item Treatment Self-regulation questionnaire,[14] (ii) patient satisfaction using the telemedicine satisfaction and usefulness questionnaire, (iii) reported side effects of medications, (iv) hypertension and stroke knowledge using a 14 item questionnaire & (v) adherence measures to medications prescribed for primary prevention and lifestyle advice (physical activity, dietary patterns, alcohol and cigarette use); and participant preferences, insights, and challenges in using the app and efforts toward adopting behavioral change collected through and end of study key informant interview.
3. **Signal of Efficacy measures**:1.) Change in total stroke risk score at month 2 calculated as difference between baseline score and month 2 score. 2) Change in stroke risk factor awareness score. 3) differences in number of encounters with healthcare provider during the period of the trial in those who have either hypertension, dyslipidemia or diabetes.

Statistical Analysis: For this pilot trial, our sample size focused on precision of estimates for a future study design rather than power of statistical tests. We will compare medians and means for continuous variables using either the Mann-Whitney's U-test or Student's t-test (paired) while categorical variables will be compared using the Chi-squared tests. A $p<0.05$ was considered significant difference between the 2 groups. Unadjusted odds ratios were calculated for primary outcome measures.

Qualitative Interviews: We will conduct key informant interviews (KIIs) with intervention participants to explore personal perspectives on acceptability of the app and video, including barriers and facilitators of its use, behavioral change efforts made to reduce stroke risk, and recommendations for revision and educational module content. Educational module content via a wireframe of app content will be shared with participants to ascertain their perceptions and recommendations for content refinement. Additionally, factors related to the social determinants of health (SDOH) will be included to better understand influence on lifestyle modification, stroke risk, and access to care and adoption of recommended health behaviors. Clinician KIIs will be completed to explore their acceptance and readiness to use the app, input of current treatment practices, recommendations for educational module content, behavioral modification strategies, clinical team educational needs, and barriers and facilitators toward intervention implementation. Interviews will be audio-recorded, transcribed and translated to English when necessary, and thematically analyzed using inductive and deductive approaches.

SIBS-GENOMICS INFORMATION SHEET AND CONSENT FORM - CASE

Title of Research**: Systemic Investigation of Blacks with Stroke-Genomics (SIBS-Genomics)**

IRB Research approval number:

Principal Investigators: Prof. Mayowa O. Owolabi MBBS, MSc, DrM, MWACP, FMCP, FAAN, FAS
Professor & Dean, Faculty of Clinical Sciences,
University of Ibadan

Prof. Bruce Ovbiagele MD, MSc, MAS, FAAN
Professor and Associate Dean, University of Califonia, San Francisco
Chief of Staff, San Francisco Veterans Healthcare System

Funded by: National Institutes of Health (NIH) USA in collaboration with
University College Hospital, Ibadan

You are being invited to participate in SIBS-Genomics, a project designed to discover, validate and functionally characterize novel genetic variants associated with ischemic stroke in people of African ancestry. We hope that you will find this information helpful.

The University of Ibadan in collaboration with a network of other Universities and research centres in Nigeria, Ghana, South Africa, UK and US is conducting a research (SIBS-Genomics) on black populations of West Africa and the US, to find out more about how lifestyle, medical conditions (eg. blood pressure and cholesterol) and genes act together to influence the development of stroke in people of black African origin. We are asking everyone who comes to this hospital/clinic with acute Ischemic stroke (within two weeks) to participate in this study. Approximately. 2,100 patients with stroke and 2,100 people without stroke in Nigeria and Ghana will take part in this study.

Why is SIBS-Genomics being done?
As you may know, stroke is the major cause of death and disability worldwide. We know that a person's chance of getting a stroke is related to lifestyles such as eating habits, level of exercise as well as exposure to tobacco smoke, blood pressure and diabetes. Scientists have also found that many genes may be linked to stroke and we expect they will find many more in the future. **Ischemic stroke is defined as** *"a spontaneous, non-traumatic, abrupt onset of global and/or focal neurologic deficit associated with brain infarction seen on neuroimaging and is not due to haemorrhage or non-vascular causes.*

The purpose of SIBS-Genomics is to discover, validate and functionally characterize novel genetic variants associated with ischemic stroke (IS) in people of African ancestry. This will substantially facilitate the understanding of the molecular mechanisms of ischemic stroke thereby enabling the emergence of a new array of targeted diagnostic/prognostic tools and interventions to reduce the burden of stroke globally and especially in African Americans in whom the burden remains disproportionately high. Please ask us questions about anything you do not understand or if you would like more information, we are happy to explain this to you more than once.

How long will this research last and how much of your time will be involved?
To meet up with our target sample size of 100 participants, the study will run for 3 months but your involvement will only last while you are admitted on the ward and for at least 1 month after the stroke episode. You may be contacted for follow-up afterwards if you wish to continue participate.

What is involved in participating in SIBS-Genomics?
We will help you to fill out a questionnaire about your health, diet, exercise, and your use of tobacco, alcohol, stress, previous medical problems, medications and your level of knowledge about stroke, hospital anxiety and depression Scale and other aspects of your health. The tests and analysis required of you are part of the harmless routine procedures needed for treating your disease condition and they include: evaluation of your blood pressure, heart rate, height, we waist and hip circumference, Carotid ultrasonography, brain scan (MRI), ECG, Echocardiography and duplex ultrasound of the vessels supplying your brain. In addition, we will need to withdraw about 30ml of blood (this is not up 3 tablespoons) which will be used to test for lipids, sugar level and genetic analysis while the other will be stored for future analyses. We will also collect abo 20ml of your urine for further analysis.

We will need less than 5 minutes to take the blood sample from a vein in your arm. They will be involved in an interview which will take about 20 minutes of their time. There will be no medicines to take and no experimental treatments to undergo in SIBS-Genomics. Nothing else is required. The only genetic testing on your blood sample will be for conditions associated with stroke.

How will information about me be kept private?
To protect your privacy, we will replace your name with a code (numbers, letters or both). We will separate your name and any other information that points to you from your blood sample and your data. We will keep files that link your name to the code number in a locked cabinet. Only permitted members of the research team will have access to these files. No one who reads or hears a report about SIBS-Genomics will be able to identify you because, before any facts are given out we combine your facts with those of other people in the study. Your name or other facts that might point to you will not appear when we present this study or publish its results.
A goal of H3Africa is to create a way for researchers to share and learn from each other especially within Africa. One of the best ways to do this is for scientists to share research data. We like your permission to share your health history, laboratory test results and your go information. When we share this information, people will not know your name. Other investigator who want to use your data (without your name) will need to first ask for permission from the central repository. They will need to agree only to use the data for a specific scientific research. There is a small chance that your data together with the data of many other people could be to develop new treatments which might be beneficial to you or other people. If this happens, it is unlikely that the proceeds will be shared with you.

What will happen to the samples?
Your blood samples will be processed in our laboratory and the result of the fasting blood sugar and lipid profile will be given during follow-up.

Voluntary nature of participation and right to withdrawal
It is a personal decision whether you take part in the study. You can say "Yes" and join the study or you can also say "No" you don't want to join. If you participate in the study, you can change your mind later and decide that you don't want to participate anymore and you do not want your blood to be used in this study. Please let us know and we will destroy the sample. If your sample has already been tested at the time you change your mind, your results and other data may have already been shared with investigators. In that case we will not be able to destroy this data. Your data can be removed from the central repository, however, that means that no additional researchers get your data.
Whether you decide to join or not to join the study, the way we look after you in this clinic will be the same. It is your decision whether to be in the study or not.

Potential Risks associated with the research
We want to tell you of the possible risk associated with this study. Most of the time when we take blood it is safe, but sometimes when we take the blood sample, people feel a bit faint or very rarely get an infection. You may also get a slight bruise where we took the blood, if it does happen you will be treated immediately without extra costs.

Potential benefits associated with the research
This study may not directly help you (or your children) to get better but we hope it will benefit others in the future. What we are trying to do is very complex and could take a long time. Whether you decide to Potential benefits join this study or not will not affect your treatment in the clinic. Your decision to join is of your own free will.
How will I find out the results of the study?
We plan to share some of the results of tests conducted during this project (e.g duplex ultrasound, blood sugar) that may contribute to your medical care with you. We will attempt to input relevant results into your medical records.

This study will take a while before it is concluded and when it is finished, observations and discoveries will be shared with other health professional through publications. However, if you have any questions, you could ask your doctor.

Are any costs or payments involved?
It does not cost you anything to provide a blood sample for SIBS-Genomics and you will not be charged for any tests required specifically for this research only. Although, you will not receive any monetary

gratification for participating in this study, you will enjoy excellent clinical care and have access to communicate issues about your health with the clinicians working with the team of investigators. We will do everything possible to avoid any degree or form or injury while undergoing clinical assessment or giving a blood sample, nonetheless we will provide adequate treatment in the very unlikely event that this occurs.

SIBS-GENOMICS CONSENT FORM-Case

Principal Investigators: Prof. Mayowa O. Owolabi MBBS, MS, DM, MWACP, FMCP, FAAN, FAS
Professor & Dean, Faculty of Clinical Sciences,
University of Ibadan

Prof. Bruce Ovbiagele MD, MSc, MAS, FAAN
Professor and Associate Dean, University of Califonia, San Francisco
Chief of Staff, San Francisco Veterans Healthcare System

Funded by: National Institutes of Health (N.L.H) USA in collaboration with
University College Hospital, Ibadan

This research which is part of the Human Heredity and Health in Africa ("H3Africa") project has been approved by the University of Ibadan/University College Hospital Ethics Committee, Ibadan and the Chairman of this Committee can be contacted at IMRAT, UCH, Ibadan, Nigeria.
Email: academic uichhric@yahoo.com

In addition, if you have any question about your participation in this research, you can contact the overall principal investigator Prof. Mayowa O. Owolabi, Professor & Dean, Faculty of Clinical Sciences, University of Ibadan, Nigeria.

Consents and Signature

I agree to participate in SIBS-Genomics. I understand that I will fill out a brief survey about my health, lifestyle, food habits, medications and knowledge about stroke. I will have about 30ml of one blood sample drawn and about 20ml of urine collected. The tests to be carried out on my samples will include cholesterol, glucose and genetic factors. I will also have my blood pressure and heart rate taken, my height, weight, waist and hip circumference measured. My medical record will be assessed for my medical and treatment information. My only discomfort will be related to the needle prick for drawing the blood, and the most common adverse effect is bruising around the vein from where the blood sample is drawn

I understand that my participation in the study is voluntary. All information gathered for this study strictly confidential and will not be used to create financial profit. I will not be identified in any published report. am free to refuse to participate or withdraw from the study at any time without jeopardizing my future care. I have been given a chance to ask questions and feel that all of my questions have been answered.

I know that giving a blood sample for this study is my choice. I understand that my individual results will not be given to me. I will receive a signed copy of this form. I have read the part of the formation Sheet about storing my blood sample for future research. My choice about having my blood sample stored and used for research under the conditions described is: (please check ONE box)

- o I agree to participate in SIBS-Genomics but do not want my sample to be shared with other Investigators outside SIBS-Genomics. I agree to participate in SIBS-Genomics and my sample can be shared with other investigators within H3 Africa only for research in a related field (e.g. cardiovascular research)
- o I agree to participate in SIBS-Genomics and my sample can be shared with other investigators in any other research field

_____
Name of Participant

_____
Name of Authorized Representative (if applicable)

_____ _____

Signature of Participant Authorized Representative Date

Consent form administered and explained in person by:

_____
Name and title

_____ _____
Signature Date

In my judgement, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

_____
__
Name of Investigator

_____ _____
Signature of Investigator Date

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT.