Stroke Minimization Through Additive Anti-atherosclerotic Agents in Routine Treatment

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RESEARCH STRATEGY

B. SIGNIFICANCE AND INNOVATION

B.1.1. Burden of Stroke among Africans: Stroke is a leading cause of mortality, disability and neuro-psychological deficits globally.[1-8,44-50] In sub-Saharan Africa (SSA) where an unprecedented rise in stroke burden is currently raging, the age-standardized stroke incidence and prevalence rates are up to 316 per 100,000 and 981 per 100,000 population respectively with a 3-year mortality rate of 84%.[51] This is in sharp contrast to the sustained declines in stroke incidence in high-income countries (HIC) over the past four decades through better awareness and control of vascular risk factors.[1,2] Indeed, in low and middle income countries (LMICs) especially SSA, stroke levies a heavy toll on the developing economy by affecting a relatively younger age group and is a major public health challenge threatening to destabilize the recent modest economic gains in most of the affected regions.

B.1.2. Contributions of Risk factors to Stroke among Africans: Globally, >90% of stroke burden is attributable to modifiable risk factors including behavioral factors such as smoking, poor diet, and low physical activity; and clusters of metabolic factors such as high systolic blood pressure, high serum lipids, and elevated fasting plasma glucose.[48] The impacts of the top 10 common risk factors for stroke worldwide were recently reported in the INTERSTROKE epidemiological study using a direct enumerated approach. [52-54] It has been posited that stroke among blacks is mechanistically driven by extracranial and intracranial atherosclerosis and small vessel disease with minimal contributions from cardio-embolic phenomena compared with the scenario in the developed world.[55-60]

B.1.3. Contributions of Contextual factors to Stroke among Africans: Several factors including fragmented/uncoordinated post-stroke care, low-levels of awareness among providers and patients about contributions of undiagnosed, under-controlled vascular risk factors to stroke recurrence, and cost of cardiovascular preventive medications, frequently challenge effective secondary risk factor control among stroke survivors in resource-limited settings.[61-66] A stroke patient hospitalized in West Africa spends an average of 170 times more in two week period than the average person spends per year on overall health.[67] *Drug expenses account for the highest portion of the cost, in part because patients are obliged to buy individual retail pharmaceutical products, having little access to generic drugs, which could reduce costs, or combinations of generic drugs which could reduce costs and improve adherence*.

B.1.4. Risk Factor Control to Prevent Recurrent Strokes: Among stroke survivors, a major source of subsequent mortality and functional decline is recurrent stroke and myocardial infarction (MI).[68-72] Prevention of future vascular events is critical to reducing the morbidity/mortality of patients with stroke, since the risk is highest within one year of the index stroke.[73,74] Antihypertensive, antithrombotic, anti-coagulant, anti-diabetic and lipid-lowering therapies form the foundation of modern secondary preventive strategies for strokes and other cardiovascular diseases.[75] Combination therapy using a statin, aspirin and antihypertensive agents has been associated with reductions in stroke, MI and mortality risk compared to monotherapy,[13] and an 80% reduction in overall cardiovascular event risk when aspirin, B-blockers, lipid-lowering drugs and ACEIs are used simultaneously.[14] Hence, most guidelines recommend that secondary prevention interventions for stroke (comprised of antihypertensive, statin and anti-platelet therapy), should be initiated promptly after stroke and adhered to in a persistent fashion to achieve the goals of risk reduction for vascular events.[11,12]

B.1.5. Stroke Prevention Evidence Practice Gap: Use of evidence-based therapies for vascular risk reduction among stroke patients receiving conventional care in LMIC is extremely low.[76] Usually an individual recovering from stroke is prescribed multiple medications to treat various risk factors indefinitely, and this often engenders poor adherence and non-persistence to these efficacious, evidence-based preventive therapies.[16-25] Indeed, reports emanating from HICs suggest that continual utilization of secondary prevention medications is challenged, with short-to-medium term persistence rates ranging between 60 to 90%. [20-25] On a global scale, a recent meta-analysis of 34 studies showed that 43% of CVD patients fail to adhere to preventive therapies in the first two years,[18] with 46% of patients on statins, 41% on antihypertensive agents and 30% on aspirin failing to adhere to their medications. Thus non-adherence, treatment complexity, pill burden, and limited expert input, are the principal antagonists militating against widespread compliance to life-saving cardiovascular prevention medication interventions, leading the WHO to advocate for interventions that will address the factors contributing to non-adherence to CVD treatments as a priority issue.[77] Moreover, the Neurologist-population ratio in SSA ranges from 1 per 162,885 persons to none in 11 countries (vs. 1 per 29,200 persons in the US)[26], underscoring the need to identify relatively simple strategies that can be applied broadly for stroke survivors in resource-constrained settings.

B.1.6. Polypill strategy for Prevention of stroke: Fixed-dose combination pills, also known as *polypills*, for cardiovascular event prevention is a strategy of combining several commonly used preventive medications into a single pill[78] for either primary or secondary prevention. Generally, most of the polypills now available are composed of a minimum of a statin, an antiplatelet drug, and an antihypertensive agent(s) and are selected based on clinical trial efficacy and pharmacological interaction data[26,79] with the objectives of improving drug adherence by reducing pill burden thereby improving risk factor control and potentially reducing vascular event risk reduction as a cost-effective intervention.[31] Feasibility studies have been coducted using polypills vs. 'usual care', with strong evidence for improved adherence,[80-82] superior or at least non-inferior efficacy in systolic BP and LDL-C control,[28,29,34,38,80-82] better acceptability[80-82] and comparable safety profile and better cost effectiveness in both LMICs and HICs.[83-86] Although these benefits are yet to translate into significantly higher reductions in hard outcomes vs. usual care, majority of the available studies have had relatively short duration of follow-up (on average 8 weeks to 6 months) whereas it has been previously established that there is at least a 12-24 months lag phase before the maximum benefits of SBP and LDL-C reduction by these medications are typically observed.[87,88]

B.1.7. Polypill Strategy for Atherosclerotic stroke management: Given that atherosclerosis mechanistically underlies the overwhelming majority of ischemic strokes, it is anticipated that polypills may halt the progression/produce a regression of atherosclerotic plaques thereby mitigating the risk of subsequent cerebrovascular diseases among stroke survivors and also positions carotid intimal media thickness measurements before and after intervention as a suitable surrogate marker of outcomes in such pilot trials. Significantly however, many of the ongoing studies on the polypills have been conducted in high-income countries with very little contribution from LMICs in SSA hence findings cannot be directly extrapolated to resource-limited settings where CVD burden including stroke is greatest. Furthermore, although there are major international polypill trials on-going[89-94], none is specifically focused on secondary risk prevention among stroke subjects resident in LMICs.

B.2. Significance: Current projections are that the already overwhelming burden of strokes and other cardiovascular diseases (CVDs) in Africa and other LMICs will continue to escalate over the coming decades as known vascular risk factors such as hypertension, dyslipidemia, obesity and diabetes burgeon in these populations due to adoption of western lifestyles, lack of awareness of the association between vascular risk factors and CVD occurrence and poor primary healthcare infrastructure for the control of non-communicable diseases.[10,95] The notion that >90% of strokes can be prevented through risk factor modification is an important impetus to understand context specific and relevant risk factors for stroke in SSA in order to stem the rising tide of stroke.[10,48,53,96] The FOA for this R21 funding mechanism cites *"the development of innovative, collaborative research projects on brain and other nervous system…, revelant to low-and middle-income countries"* and also *"lack of adequate prevention and treatment in LMICs is a major contributor to the burden of disease and disability".* Identifying strategies to reduce vascular risk in LMIC could meet a global goal of reducing chronic disease death rates by an additional 2% per year, with only a moderate rise in health expenditure.[63] Thus the overarching objective of the **S**troke **M**inimization through **A**dditive **A**nti-atherosclerotic Agents in **R**outine **T**reatment (**SMAART**) trial in response to the NIH FOA (PAR-11-031) is to assess in a phase 2 pilot/pragmatic RCT, whether a polypill containing fixed doses of 3 antihypertensives, a statin and antiplatelet therapy taken once daily orally would result in carotid intimal thickness regression-a surrogate marker of atherosclerosis, improved adherence and tolerability compared with 'usual care' group on separate, individual secondary preventive medications among Ghanaian stroke survivors in a single center study. A 12-month follow up is planned to allow sufficient time to assess sustainability of adherence to the polypill, overcome the time-lag effect required for translation of the CVD prevention benefits of SBP and LDL-C control and initiate the collection of 'hard cardiovascular outcome measures' such as recurrent strokes and vascular events to inform the design of a larger future phase 3 SMAART trial to assess these clinical outcomes in a multi-center study. SMAART will also incorporate building of institutional and human research capacity for the conduct of interventional studies centered around evaluating outcomes of stroke. It is notable that SMAART involves several early stage SSA investigators (Sarfo, Osei, Appiah), which is key for building sustainable human capital and clinical trial research capacity in SSA. Findings from the SMAART study will undoubtedly contribute meaningful data from the African perspective towards the formulation of guidelines for global adoption of polypills into routine care for secondary CVD risk prevention by international bodies such as the World Health Organization. In the long-term, findings from SMAART could serve as a scalable strategy for managing CVD risk among stroke survivors in SSA, and even other LMICs.

B.3. Innovation: There are six major RCTs on polypills currently on-going or planned, three of these RCTs-TIPS-3,[89] HOPE-3,[90] and HOPE-4,[91] are primary prevention studies, two of them-PROPS[92] and SECURE[93] are secondary prevention trials and PolyIran study[94] is aimed at both primary and secondary CVD prevention. The innovative aspects of the SMAART trial include: ***First,*** this will be to our knowledge the first study to evaluate the feasibility of a polypill on secondary risk reduction among stroke survivors in resource-limited SSA setting with the potential to generate results that will inform research agenda and policy on the utility of the polypill in other LMICs. ***Second***, although SMAART is a phase 2 study, a medium to long-term follow-up of 48-weeks is planned to allow investigators to assess changes in the carotid intima-media thickness, a US Food and Drug Administration approved and validate surrogate marker of CVD risk as a primary outcome measure,[97-99] and compositely assess the sustainability of adherence to the polypill in LMICs as well as collect preliminary data on blood pressure and lipid control and cardiovascular events. Finally, even if SMAART were not to meet its primary endpoint, we will collect substantive data on feasibility, tolerability, adherence, risk factor control estimates, quality of life, and functionality, which could inform the design and conduct of future studies of the polpypill strategy for high vascular risk individuals in SSA.

C. PRELIMINARY DATA AND PREVIOUS WORK

C.1. Questionnaire for Verifying Stroke Free Status in Ghana: To assure accurate exclusion of stroke mimics, we developed a pictographic version of the Questionnaire for Verifying Stroke Free Status with superior diagnostic properties including 98% certainty for determining stroke-free status, which was validated in 3 languages commonly spoken in West Africa (including Ghana). [100,101]

C.2. Stroke types, severity, and outcomes in Ghana: In a study of stroke patients in Ghana and Nigeria, we recruited 3,000 case-control pairs. 64.4% of strokes were ischemic, 35.6% were hemorrhagic.[102] Of the ischemic strokes, 45.5% were small vessel, 35.5% were large-artery atherosclerosis, and 14.0% were cardio-embolic. [102] Topmost risk factors for stroke in descending order of Population Attributable Risk (PAR) were hypertension (Adjusted OR, 95%CI: 10.72,7.30-15.76), diabetes mellitus 2.24 (1.71-2.94), dyslipidemia 1.89 (1.48-2.41), and cardiac diseases 1.75 (1.22-2.50).[102]

C.3. Inadequate Risk factor control at one year after stroke in Ghana: We analyzed data on stroke survivors seen at the Neurology Clinic of Kwame Nkrumah University of Science and Technology (KNUST) in Kumasi, Ghana (site of this proposed study). We found that at baseline 89.8% had hypertension, 23.5% had dyslipidemia and 20.2% had diabetes mellitus. [41] At one year after the index stroke: i) systolic blood pressure (SBP) levels were not within guideline recommended targets in one-third of patients, ii) ~ 2-3 antihypertensive medications were required by most patients, iii) 30% were not on statin treatment, iv) 35% were not on antothrombotic therapy.[41,42]

C.4. Benefit of Optimal Combination Preventive Drug Treatment on vascular risk reduction after stroke: We analyzed a dataset for an international multicenter secondary stroke prevention trial involving 3,680 recent ischemic stroke patients to assess the effects of optimal combination of evidence-based drug therapies including antihypertensive agents, lipid modifiers, and antithrombotic agents on the risk of recurrent vascular events after stroke. Patients were categorized by appropriateness level 0 to III depending on the number of drugs prescribed divided by the number of drugs potentially indicated for each patient (0=none of the indicated medications prescribed and III=all indicated medications prescribed). We found that compared with level 0: the adjusted hazard ratio of recurrent stroke for level I was 0.51 (95% CI, 0.21-1.25), level II 0.50 (0.23-1.09), and level III 0.39 (0.18-0.84) and similarly for the composite risk of stroke/coronary heart disease/vascular death strongly highlighting that optimal combination of secondary prevention medication classes after a recent non-cardioembolic stroke is associated with a significantly lower risk of stroke, major vascular events, and death.[15]

C.5. Polycap: In the SMAART study we will be procuring study medications from Cadila Pharmaceuticals, manufacturer of Polycap® (combination of 5 drugs at low doses - aspirin, 100 mg; atenolol, 50 mg; ramipril, 5 mg; thiazide, 12.5 mg; simvastatin, 20 mg). Polycap reduced systolic blood pressure by 7.4 mm Hg (95% CI 6.1-8.1) and diastolic blood pressure by 5.6 mm Hg (4.7-6.4), which was similar when three blood-pressure-lowering drugs were used. Reductions in blood pressure increased with number of drugs used (2.2/1.3 mm Hg with one drug, 4.7/3.6 mm Hg with two drugs, and 6.3/4.5 mm Hg with three drugs). Polycap reduced LDL cholesterol by 0.70 mmol/L (95% CI 0.62-0.78), which was greater than for groups without simvastatin ($p<0.0001$). Tolerability of Polycap was similar to that of other treatments, with no evidence of increasing intolerability with increasing number of active components in one pill.[43] *For the SMAART trial, participants in the polypill arm will receive **2 capsules of Polycap® daily** in order to be in close accord with published evidence[103] and secondary prevention guideline recommended doses for statins after stroke[11] and in recognition of the higher*

and more refractory blood pressure levels encountered in patients of African ancestry.[104,105] Moreover, two capsules of Polycap® daily reduces BP and LDL cholesterol to a greater extent vs. one capsule, with similar tolerability. [106] We will purchase a year's supply of Polycap® (twice daily) for use in SMAART from Cadila Pharmaceuticals & obtain approval for its evaluation in SMAART from the Ghanaian Foods & Drugs Board.

C.6. Relevant Expertise and Experience (Individual and Collective) of Key Personnel:

a] **Dr. Nichols (SMAART PI) is Assistant Professor at the Medical University of South Carolina in the College of Nursing. She is actively engaged with individuals, families, and community stakeholders to reduce health disparities and improve health outcomes among underserved, vulnerable populations within rural, urban, and global communities. Currently, she is involved with stakeholders from several organizations in South Carolina developing community-based research approaches to address health disparities among African American communities and am collaborating on studies in sub-Saharan Africa to address the disparities they face in preventing and treating non-communicable diseases. As a Registered Nurse with 25 years of clinical experience, her work focuses on health promotion, disease prevention, and management, especially in the areas of cardiometabolic conditions, such as diabetes, obesity, hypertension, and stroke. Recently, she was awarded a global health pilot grant, in collaboration with a Ghanaian partner, to explore the use of mobile health technology and task-shifting among individuals with diabetes in Ghana. She is experienced in both quantitative and qualitative research methodologies and specialize in qualitative and mixed method approaches.** b] **Dr. Ovbiagele** (SMAART ~~Co-PI~~Co-PI) is Associate Dean of the Medical School at University of California San Francisco and the Chief of Staff at the VA with experience in development/implementation of interventions targeted at CVD risk reduction in vulnerable populations,[107,108] and has been involved in several stroke trials. He has served as Vice-Chair of the Committee that wrote the prevailing practice guidelines on secondary stroke prevention.[11] He currently leads the "Tailored Hospital-based Risk Reduction to Impede Vascular Events After Stroke" (NCT01900756),[109,110] which incorporates a chronic care model-based intervention to improve post-stroke outcomes and "Phone-based Intervention Under Nurse Guidance After Stroke (PINGS)" (NCT02568137),[111, 112] that combines mHealth with task shifting components among stroke patients. c] **Dr. Sarfo** (SMAART MPI) is a consultant neurologist and a double PhD holder in molecular medicine and epidemiology with expertise in the conduct of several prospective cohort and randomized controlled trials at the Kwame Nkrumah University Teaching Hospital. He has set up the first stroke unit in the middle and northern belts of Ghana and a neurology clinic serving an estimated population of 10 million Ghanaians. Dr. Sarfo is the site co-investigator for the SIREN (HG007479),[113] and PINGS feasibility RCT on m-health interventions to improve blood pressure control among stroke survivors in Kumasi, Ghana. c] **Collaborations:** Our investigators have been involved in several projects of direct relevance to SMAART research focus. Three SMAART investigators (Ovbiagele, Sarfo, and Appiah) are all involved in 3 distinct NIH-funded studies in West Africa: i) a pilot RCT of an mHealth intervention among stroke survivors in Ghana (NS094033) to decrease risk factors for recurrent stroke; ii) a case-control research project, which investigates genetic and environmental risk factors for stroke among people of African ancestry (HG007479), iii) a case-control study (NTW010479) characterizing the presence of vascular risk [using CIMT as primary outcome] among 240 HIV subjects on cART (vs. 240 cART-naïve HIV patients and 240 HIV-uninfected subjects).

D. APPROACH

D.1. Overview: The overarching objective of the Stroke Minimization through Additive Anti-atherosclerotic Agents in Routine Treatment (SMAART) trial is to assess whether a polypill containing fixed doses of 3 antihypertensives, a statin and antiplatelet therapy taken once daily orally would result in carotid intimal thickness regression, improved adherence, and tolerability compared with 'usual care' group on separate individual secondary preventive medications among Ghanaian first time stroke survivors. Our ultimate objective is to design of a future multi center, double-blinded, placebo-controlled, parallel-group, RCT comparing the clinical efficacy of the polypill strategy vs 'usual care' in the African context to derive locally relevant, high-quality evidence for routine deployment of polypill for CVD risk moderation among stroke survivors in LMICs.

D.2. Design: SMAART incorporates (i) a pilot randomized controlled trial and (ii) a human capital/institutional capacity building component. We propose a randomized, open label, blinded endpoint clinical trial with the intervention arm assigned to a polypill containing 3 antihypertensives, a moderate/high-intensity statin and Aspirin to be taken orally, once daily in the form of two hard capsules compared with the 'usual care' arm who will continue to take separate, individual secondary preventive medications as prescribed by their physicians. We will assess CIMT changes as a robust intermediary outcome measure for CVD events, adherence, tolerability, and risk factor control rates. Furthermore, a cadre of emerging investigators from Ghana will benefit from the rich

learning environment to be created through the implementation of the RCT and the interactions (2 years) with experts from the Medical University of South Carolina.

D3. Setting and Study Populations: SMAART will be conducted at the Komfo Anokye Teaching Hospital (KATH), a tertiary referral center and teaching hospital with 1,000 beds[114-116]. There is a stroke unit and a neurology out-patient services. Stroke survivors encountered at *Family Medicine, Internal Medicine and Neurology outpatient clinics* will be enrolled into the trial to capture usual care experiences of stroke patients as well as the use of the polypill in these diverse settings. Each year, on average 450 stroke survivors are discharged from the hospital and approximately 300 stroke survivors are seen at either the Neurology/Internal Medicine/Family Medicine clinics at KATH, and, so the proposed sample size of 120 in one year for the SMAART trial can be realized within the time frame of the grant. Of note, in the ongoing SIREN trial, KATH is fastest and highest enrolling site with 600 eligible stroke suvivors enrolled over 2 years in the 12-site two country (Ghana and Nigeria) study network.[113]

D.4. SMAART (Specific Aims 1 and 2):

- To evaluate whether a polypill-based treatment strategy vs. usual care will result in carotid intimal media thickness stabilization/regression among recent stroke patients at one year after an index ischemic stroke. (Aim 1)
- To evaluate whether a polypill-based treatment strategy vs. usual care will improve vascular risk reduction drug adherence and tolerability among recent stroke patients at one year after an index ischemic stroke. (Aim 2)

D.4.1. Study Design: SMAART is a phase II randomized, open label, blinded endpoint clinical trial to evaluate the effect of a polypill taken once daily orally in improving CMIT regression and adherence to secondary risk reduction drug intake vs. 'usual care' group with separate individual secondary preventive medications among Ghanaians with recent onset stroke/TIA in a single center study.

D.4.2. Participants: The participants will include 120 adult Ghanaian recent stroke/TIA patients (within two months of stroke onset) meeting inclusion/exclusion criteria who will be randomly assigned to either intervention or usual care arms.

D.4.3. Inclusion Criteria: 1. Above the age of 18 years; male or female; 2. Stroke/TIA diagnosis no greater than two months before enrollment. Ischemic strokes including lacunar, large-vessel atherosclerotic, cardio-embolic subtypes are eligible 3. Subjects with stroke may present with at least one of the following additional conditions: Documented diabetes mellitus or previous treatment with oral hypoglycemic or insulin; documented hypertension >140/90mmHg or previous treatment with anti-hypertensive medications; Mild to moderate renal dysfunction (eGFR 60-30ml/min/1.73m^2); Prior myocardial infarction 4. Legally competent to sign informed consent.

D.4.4. Exclusion criteria: 1. Unable to sign informed consent, 2. Contraindications to any of the components of the polypill, 3. Hemorrhagic stroke, 4. Severe cognitive impairment/dementia or severe global disability limiting the capacity of self-care, 5. Severe congestive cardiac failure (NYHA III-IV), 6. Severe renal disease, eGFR <30ml/min/1.73m2), renal dialysis; awaiting renal transplant or transplant recipient, 7. Cancer diagnosis or treatment in past 2 years, 8. Need for oral anticoagulation at the time of randomization or planned in the future months, 9. Significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation) 10. Nursing/pregnant mothers, 11. Do not agree to the filing, forwarding and use of his/her pseudonymized data.

D.4.5. Recruitment of study subjects: A total number of 120 patients will be randomized (1:1) to treatment arms. Patients with stroke meeting inclusion/exclusion criteria will be recruited from the Family Medicine, Internal Medicine and Neurology outpatient clinics at KATH. Randomization will take place within 8 weeks of the index event (ischemic stroke) in a 1:1 ratio to one of the two arms: Polypill versus Usual care.

D.4.6. Randomization Procedure: Randomization of subjects in blocks of four will be conducted by a statistician (Dr. Jenifer Voeks- PI) using a computer-generated random sequence of numbers. Consented participants will be assigned to either study arm at the baseline visit using the computer generated randomization sequence. The randomization sequence uses a minimization algorithm to ensure balance of prognostic factors such as stroke severity, average of 3 recorded baseline systolic BP measurements, & whether or not they are on background BP lowering agents, lipid modifiers & antithrombotic agents. Each sequence generated will be kept concealed in an envelope which will be opened by the Research Coordinator in the presence of the consenting study participant at enrollment.

D.4.7. Study protocol: The diagnosis of stroke will be defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death. Patients meeting eligibility criteria will be allocated to the experimental or active comparator arm. Patients allocated to the experimental arm will receive Two (2) (Polycap ®) taken orally once a day. Patients allocated to the usual care arm will receive standard of care therapies for secondary prevention with drugs and doses left at the discretion of the treating physicians. Patients assigned to Polypill will have their antihypertensive agents, lipid modifiers and anti-thrombotic agents withdrawn & replaced with the Polypill if they are already receiving such treatments before enrollment. Since our focus is to *isolate the effect of the polypill strategy itself & create equipoise*, at study inception providers for patients in both study arms will receive a brief one-time (Skype-based) training & a one time email synopsis on guideline recommended biomarker targets after stroke.[11]

D.4.7.1. Screening/run-in period-4 weeks: All potentially eligible participants referred to or who contact the study team directly will undergo screening to determine eligibility using the pre-specified criteria (see Human Subject Protection document).

D.4.7.2. Enrollment evaluation: Information on stroke type from a cranial CT scan performed within 10 days of stroke symptom onset will be reviewed by the MPI (FSS), stroke subtype information where available will be sought to classify ischemic stroke using the TOAST classification[117] into cardio-embolic, large-artery and lacunar ischemic stroke. Stroke severity and functional status at enrollment will be assessed using the modified NIHSS[118] and Modified Rankin Score,[119] followed by a detailed assessment of vascular risk factors namely hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, cardiac diseases (atrial fibrillation, ischemic heart diseases, cardiomyopathies), from history and physical examination. Blood samples for baseline assessments of renal and liver function tests, lipid profile and HBA1C will be collected and contraindications for study medications assessed. All concomitant medications will be recorded in the case report form.

D.4.7.3. Follow-up and Outcome Evaluations: Participants will be followed for 12 months with scheduled visits at months 1, 3, 6, 9 and 12 for clinical assessments and primary, secondary and tertiary/feasibility study outcome evaluations as shown in ***Table 1***.

D.4.7.4. Management of Possible Treatment related side effects: Participants who experience side-effects will be reviewed by their physicians to assess severity and appropriate measures instituted.

D.4.7.5. CIMT Assessment: Primary endpoint will be CIMT burden. Each study participant will undergo Carotid Doppler ultrasonic evaluation at baseline and month 12 for evidence of clinical or sub-clinical carotid artery disease- a validated surrogate marker of atherosclerosis.[97]To achieve reliable ultrasonic measurements of the common carotid artery IMT a standardized protocol and strict quality control procedures will be followed by *two local experienced sonographers* who will be blinded to the participants group status and risk factor levels to ensure we achieve unbiased results.[98,99] CIMT will be measured at 1 cm portions of the distal left and right common carotid artery far walls with a linear transducer (transducer frequency of 7.5 MHz) with axial resolution of 0.10mm, and calculated automatically over 3 cardiac cycles following the Mannheim consensus.[99] Average thickness of left and right carotid arteries will be used as outcome measure. We have experience in measuring CIMT as a primary outcome in our EVERLAST study (NTW010479).

D.4.8. Outcome measures:

Table 1. Definitions of Primary & Secondary Outcome Measures to be assessed in SMAART Trial.

Variable	Brief Description
Carotid Intimal Media Thickness ***Primary Outcome Measure***	End of study CIMT value will be subtracted from baseline CIMT value & divided by length of follow-up & the rate of change in CIMT (mm/yr) between treatment arms & change in intima-media (artery wall) thickness and extent of atherosclerotic plaques in the carotid artery bifurcation measured.
Change in Adherence to therapy ***Secondary outcome measure***	This will be measured at baseline and at month 12 clinic visits using the self-reported Morisky-Green questionnaire(MAQ)[120] and pill count. Patients have to meet both criteria for adherence at the in-person visits to be considered adherent.
Safety & Tolerability Indicators ***Secondary outcome measure***	Renal function: Serum creatinine measurements to calculate eGFR using the CKD-EPI[121] formula at baseline and months 1 and 12. Liver function: Elevations in liver enzymes will be assessed, if AST or ALT rises >5x Side effects profile: Adverse events will be closely monitored & side effects will be documented according to the NIH/NCI Common Toxicity Criteria[122] Discontinuation of medications: Reasons and clinical indications for stopping treatment in both arms will be compared in both arms. Regimen adjustments: Reasons for modifications in dosages including addition of new CVD agents, will be assessed in both treatment arms.
Health-related Quality of Life	The EQ-5D questionnaire[123] will be used to assess state of health of study subjects at baseline and Month 12.
Change in Patient Satisfaction	The treatment Satisfaction Questionnaire[124] for Medication will be administered at baseline and month 12.
Cognitive Dysfunction Indices	The Montreal Cognitive Assessment (MOCA) scale[125] will be used to assess global cognitive dysfunction at months 0 and 12.
Functional Status	Functional status after stroke will be assessed using the modified Rankin scale with a score from 0 to 6.
Depression	Depression will be assessed using the Beck Depression Inventory and Hamilton Rating Scale for Depression at months 0 and 12.[126,127]

CVD Risk Factor Control ***Tertiary/feasibility***	1. Blood pressure control will be defined as Systolic BP <140 mmHg and/or diastolic DP <90mmHg or (>135/85mmHg in diabetes patients). Mean change in SBP at month 12 from baseline will be compared in the two treatment groups. 2. Dyslipidemia: control will be defined by change in mean LDL-cholesterol <100mg/dl or <70mg/dl. Mean change in LDL-C at month 12 from baseline will be compared in the two treatment groups.
Incidence of Adverse events ***Tertiary/feasibility***	1. Recurrent stroke: fatal/ severely disabling stroke or non-fatal stroke; Coronary Artery Disease: Acute STEMI/NSTE deaths 2. Re-hospitalization for any CV cause; All-cause mortality

D.4.9. Sample size justification: The end of study CIMT value will be subtracted from the baseline CIMT value and divided by the length of follow-up. The rate of change in CIMT (mm/yr) between treatment arms will be tested with a two sided t-test. The rate of change in common CIMT in treated patients is around 0.085 mm/yr with a standard deviation of 0.035.[128] We assume that polypill improvement leads to a halting of CIMT progression with an assumed rate of change of 0.0825 mm/yr. With a two sided alpha of 0.05 and a 90% power we need 82 patients (104 patients with 20% drop-out rate).

D.4.10. Statistical analysis plan: Prior to addressing each hypothesis, univariate descriptive statistics and frequency distributions will be calculated as appropriate for all biological variables (including gender, age) comparing individuals by treatment arms (Polypill arm vs usual care arm). Briefly, box plots will be used to examine the relative distribution of variables stratified by treatment arm. Non-parametric and equivalent parametric statistics will be utilized to compare groups. Appropriate regression models (linear regression for continuous outcomes such as carotid-media thickness; Cox-proportional hazards regression for time to event measures such as recurrent strokes, CVD events, deaths and defaults) will be used to estimate the association of covariates with each outcome. When building models for each specific aim, the first stage of the model building algorithm will involve testing if the individual covariates are correlated with the main outcome variables. A liberal alpha=0.20 will be used for these unadjusted analyses. [129] Once the initial pool of candidate predictors has been identified, regression models consisting of multiple covariates will be fitted to identify potential confounders and effect modifiers. To achieve unbiased and robust results, optimal combinations of predictors, including interaction effects, will be identified and used for further analysis based upon whether or not they are a confounder, by whether they did not improve the model fit, or increased the standard error of the parameter estimate of the primary covariates. Finally, each model will be rigorously assessed for collinearity and goodness of fit using residual analysis. Model diagnostics will be performed using tools (in SAS or STATA) that detect outliers and influential data points. We will use diagnostic measures such as residual deviance, the hat matrix diagonal and residual chi-squared deviance and the difference between chi-square goodness-of-fit when an observation is deleted.[130] Plots of these against predicted values will be used to investigate the influence of each data point on the model. We will handle missing data using several techniques including multiple imputation and propensity score methods.[131,132]

D.4.11. Data Safety Monitoring Board (DSMB): A DSMB comprised of three experienced external experts will meet twice per year to review the safety, ethics, and outcomes of the study.

D.5. Specific Aim 3:

- To increase research capability and provide continuous mentorship to Ghanaian co-investigators

D.5.1. The SMAART trial will serve as an excellent platform to collaboratively work with the Ghanaian team: ***i)*** Training and learning on implementation of clinical trials via bi-weekly Skype team meetings). ***ii)*** Training in scientific manuscript writing for young co-investigators such as Osei and Appiah via co-authorship on presentations (n=4) and papers (n=3), and future grants (n=1+). ***iii)*** Supervised involvement in taking courses in the MUSC CTSA / Center for Global Health web based program in clinical research, which is free for members of grant funded study teams at MUSC and offers courses including *Clinical Epidemiology, Clinical Biostatistics, Regression Methods for Clinical Research, Grants Overview, Critical Review of the Literature, Ethical Issues in Clinical Research and Clinical Trials*.
iv) Developing editorial capabilities of Dr. Sarfo via participatation in the editorial processes of eNS and ISC. Dr. Ovbiagele is the Founding Editor-in-Chief of eNeurologicalSci (eNS), a peer review journal of the World Federation of Neurology. He is also chair of the program committee for the International Stroke Conference (ISC), the premier scientific stroke meeting in the world. Participation by Junior Ghanaian co-investigators in these proposed activities will be monitored to build their research experience, foster career development, and enhance networking beyond this specific research project.

E. ANTICIPATED CHALLENGES

1) Subject Accrual: Assessment visits will be scheduled, whenever possible, on days subjects already have scheduled clinic visits or plan to visit the stroke patients who may be incapacitated. **2)** Meeting sample size:

There is a high case load of stroke patients with approximately 700 cases per year. At a recruitment rate of 5 cases per week, recruitment of 120 stroke patients meeting eligibility criteria is a realistic objective. **3)** Missing Data: We anticipate there may be missing data due to loss to follows but we will minimize this by home visits where geographically feasible, providing transportation stipends and employing statistical methodology to account for missing data.

F. TIMELINE OF ACTIVITIES:

Activities	YEAR 1				YEAR 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Ethics approval and renewal at KNUST and MUSC	X				X			
Hire, orient and train project staff	X							
Data collection instruments & questionnaires	X							
Study subject recruitment and follow-up		X	X	X	X	X	X	X
Training and human capacity building	X	X	X	X	X	X	X	X
Prepare manuscripts, final reports, & grant		X		X		X		X

F.1. Dissemination: Yearly reports on progress will be shared with the NIH. Findings from the research study will be disseminated by submitting abstracts and poster presentations at conferences such as the International Stroke Conference and through multiple manuscripts to be published in Open-access journals and results will be disseminated to research participants.

F.2. Expected Outcomes, Benefits, and Impacts- Translation & Scaling Up: SMAART will be the first study in Africa to provide pilot data on the safety, feasibility, tolerability, risk factor control rates and intermediate CVD outcome (CIMT) of a polypill strategy for secondary prevention after stroke. The highest risk for recurrent stroke and CVD events occurs within the first year after stroke and the SMAART intervention is targeting this phase to provide prelim data for a future multi-site, multinational study to be conducted across resource-limited centers to evaluate hard CVD events and cost-effectiveness of the polypill, specifically for stroke survivors.