Phone-based Intervention Under Nurse Guidance After Stroke 2 (PINGS 2)
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RESEARCH STRATEGY

BACKGROUND AND SIGNIFICANCE

B.1. Burden of Stroke: Stroke is a major contributor to death, disability, and dementia.[6-8,47] Beyond the personal toll, costs (direct expenditures & lost productivity) related to stroke are prohibitive.[48] About 25% of strokes are repeat occurrences, leading to further major functional decline & subsequent risk of mortality.[49-54]

B.2. Burden of Stroke in Low- and Middle- Income Countries (LMICs): LMICs currently bear the greatest burden of stroke on the globe with recent trends suggesting that sub-Saharan Africa (SSA), in particular, now bears the highest stroke rates worldwide with age-standardized stroke incidence rates of 316 per 100,000, prevalence rates of 14 per 1000 population, 1-month mortality of up to 40% & a 3-year mortality rate of 84%.[20-23] Strokes in SSA affect predominantly a young age group & is associated with profound diminution in quality of life, via stigmatization,[55] depression,[56] & vascular cognitive impairment[57] in proportion to the severity of functional deficits. Whilst stroke rates are declining in High-Income Countries (HICs) through improved vascular risk factor control, the burden of stroke is projected to escalate in LMICs in the coming decades due to an astronomical rise in vascular risk load engendered by adoption of westernized lifestyles.[2-10]

B.3. Gaps in Stroke Preventive Care in LMICs: Several factors work against favorable outcomes for stroke survivors in LMICs including (i) perennial lack of expertise to coordinate & implement evidence-based interventions for secondary prevention. For instance, the neurologist-to-population ratio is 0.3/1,000,000 in Africa[19] & these neurologists predominantly work in major cities & (ii) limited access to post-stroke care due to geographical & financial barriers in a setting where a significant proportion of the population resides in remote village dwellings.

B.4. Ameliorating the Burden of Stroke: Stroke (including recurrent stroke) is highly preventable via risk factor control.[3,58] By far the most powerful modifiable stroke risk factor is hypertension (HTN),[59,60] and uncontrolled HTN after a stroke is a major predictor of recurrent stroke.[49-53, 61] Sub-optimal HTN control poses a serious challenge for stroke prevention. Among stroke survivors, achieving consistency of blood pressure (BP) control lowers risk of recurrent stroke, myocardial infarction, and other vascular events.[62,63] However, less than one third of recent stroke survivors have BP controlled ≥ 75% of the time.[63]

B.5. Impact of HTN on Stroke Occurrence in LMICs: Improved control of HTN and other vascular risk factors achieved in HICs has led to a significant reduction in stroke burden, unlike in LMICs.[2-10] Indeed the effect size of HTN and stroke occurrence among Africans is the highest in recorded literature.[11] HTN is often uncontrolled in a significant proportion of the adults in LMICs. This is likely due to a cluster of potentiating factors including cultural beliefs & misconceptions about HTN, unavailability of health facilities, lack of health personnel, lack of access to antihypertensive medications, and so forth.[12-18] The concept of chronic medical therapy requiring life-long treatment using antihypertensive therapy and other secondary preventive therapy after stroke in LMICs is a real challenge engendering increased risk for stroke recurrence & mortality.

B.6. Barriers to HTN Control after Stroke: The typical stroke patient has associated co-morbidities that require polypharmacy (even control of BP alone may require 3 distinct drugs).[42,43] Thus, the combination of the need for dedicated follow-up and the chronicity of post-stroke treatment is an inherent wellspring for fragmented healthcare. So although sustained adherence to HTN medications can control HTN and reduce stroke events,[64-66] lack of adherence is a leading modifiable barrier to BP control.[15,67-69] Also, failure to intensify therapy in a timely manner (i.e., therapeutic inertia) also results in poor control.[25,27] Three reviews of 133 RCTs ([37 RCTs],[27] [78 RCTs],[25] [18 RCTs],[26]) involving HTN patients concluded *BP self-monitoring, medication reminder tactics (live or automated phone calls) and education/counseling*, individually and/or in combination, often improve adherence, reduce therapeutic inertia and result in significant BP declines.

B.7. Solutions to HTN Control after Stroke: Developing a culture of preventive health care is imperative for the future of health care delivery, particularly in underserved regions of LMICs. As chronic disease patients are actually often their own primary carers, their needs and preferences must be taken into account in the development of management plans.[70] Therefore, encounters between patients and their health care professionals become a critical intersection for information exchange, decision-making and motivation.[71] Stroke is a prime example of a common chronic disease that causes substantial morbidity and mortality and requires long-term medical management and coordinated support. The majority of such care would occur in outpatient settings where well-established clinical practice guidelines can be used to guide treatment decisions. It is believed that informed patients improve their decisions by collaborating with their healthcare providers toward a common goal. This results in increased patient involvement leading to a positive effect on the health outcomes.[72] The Chronic Care Model (CCM) acts as a guide to design interventions to improve complex care for patients with chronic disease. The six CCM components are self-management support, clinical information systems, delivery system redesign, decision support, health care

organization, and community resources. Most CCM-based interventions have shown significant improvement of a care process or outcome measure and reduction of health care costs.[73-79] *A key CCM component* consists of supporting patient self-management to improve self-efficacy, the confidence in one's ability to behave in a way that produces the desired outcome.[76,77] Self-BP measurement improves patient compliance with antihypertensive therapy,[78] and a systematic review of self-management programs among patients with diabetes, asthma, and HTN found improvements in relevant physiologic outcomes.[79]

B.8. Mobile Health: Efficacious, feasible and sustainable BP control programs after stroke are needed.[80] Mobile health (mHealth) technology may offer a promising approach for enhancing BP control after stroke.[33,36] mHealth tools provide an easy-to-use self-management framework that facilitates increased adherence to medical regimens (e.g., medication adherence, BP self monitoring) and timely bidirectional communication between patients and providers when warranted (e.g. regimen nonadherence, medication side effects, medication titration needs, etc.).[33,36] This technology is relatively inexpensive, provides real-time feedback to boost patient self-efficacy and sustained engagement. Two large RCTs have demonstrated the efficacy of remote monitoring of BP via mHealth in improving BP control among hypertensive patients encountered in General Practices in the United Kingdom. [81,82] An RCT of automated adherence support program delivered by SMS text message among South African hypertensive adults showed modest reductions in systolic BP at 12 months.[83] Two other RCTs conducted specifically among stroke survivors outside SSA using mhealth to improve medication adherence[84] and task shifting interventions involving nurses[85] both reported enhanced BP control.

B.9. Mobile Health for HTN control after Stroke in SSA: mhealth technology is an especially promising strategy worth pursuing for the control of HTN in SSA because there has been an astronomical expansion in telecommunication infrastructure over the last two decades with internet services and mobile phone penetration reported to be about 75% among adults and about 35% ownership of Smartphones with further increases expected as costs of mobile phone devices drops.[86,87] According to the World Bank[88], there are 136 mobile cellular subscriptions per 100 people in Ghana which is higher than subscriptions for the U.S. (126 per 100 people). Ghana's mobile subscription use is estimated to be 40 million by 2020 with one third of the population having access to the internet via smart phone usage.[88] This suggests that mhealth technology may be an acceptable platform for self-management of HTN in this low resource setting.

B.10. Patient & Provider Perspectives on mHealth for BP control after Stroke in SSA: Using an NIH R21 funding, our group demonstrated feasibility & preliminary efficacy of implementing a mhealth intervention for BP control among stroke survivors under nurse guidance in Ghana.[89] *Lessons learnt from user- and provider- feedback from our pilot study strongly advocated for an mHealth intervention for BP control after stroke of lower level of sophistication for improved acceptability and compliance.* Stroke survivors preferred (i) home self-monitoring of BP with once or twice weekly BP measurements; (ii) ability to contact a nurse via a phone call for prompt guidance when BP control is out of range, (iii) use of phone alarms set to serve as daily reminders for medication intake, (iv) due to low literacy levels, patients preferred stroke/hypertension health education content to be delivered as audio messages in local dialects instead of text messages in English. (v) Clinicians preferred being contacted by stroke patients via a phone call or text message when BP control was not optimal. They found review of automated daily BP recordings cumbersome. *These suggestions by users of PINGS intervention would obviate the need for smartphones, a specific App, & internet connectivity to support the intervention.* Of note, among Ghanaian stroke survivors completing an mHealth survey in a medical facility, **76% owned a mobile phone with internet connectivity**. Thus, a reductionist approach that considers the local context but maintains the essence of the PINGS intervention namely BP self-monitoring, medication reminders, & health education under nurse-guidance may be a feasible, implementable and sustainable strategy for post-stroke self management of hypertension in Ghana with high mobile phone penetration but low smartphone usage.

B.11. Task Shifting to Nurses*:* Another potential solution to limited healthcare access in SSA is task-shifting, i.e. training non-physician healthcare workers to perform tasks traditionally undertaken by physicians.[90] Task-shifting can potentially result in cost and physician time savings without compromising the quality of care or health outcomes for patients.[91-95] The WHO in consultation with a wide range of experts has formulated a set of 22 recommendations that provide guidance to the task-shifting approach.[96,97] One study evaluated the effectiveness of this program among 2397 patients with uncontrolled HTN in community health centers in Nigeria. Systolic & diastolic BP decreased significantly in favor of the intervention.[98] Nurse-led clinics for a variety of disease entities are among the most efficacious strategies to improve vascular risk management and several other chronic medical disorders in SSA.[99-117] However, implementation of nurse-led programs for BP control after stroke have not been tested for impact through controlled trials in SSA.[41]

B.11. Innovation: Key innovative aspects of the proposed **P**hone-based **I**ntervention under **N**urse **G**uidance after **S**troke (PINGS-2) study are - ***Firstly***, PINGS-2 has a *hybrid study design* that aims to (1) assess the clinical effectiveness of a nurse-led, multi-component, evidence-based self-management intervention for BP control adapted for stroke survivors namely (i) domiciliary self-monitoring of BP, (ii) phone-based medication reminders & (iii) patient education; and (2) develop an implementation strategy for routine integration and policy adoption of the PINGS intervention for vascular risk factor control in Ghana. Indeed, it has been suggested that "the speed of moving research findings into routine adoption can be enhanced by considering ***hybrid study designs*** that combines elements of effectiveness and implementation research."[118] ***Secondly***, PINGS-2 will be the first large, multicenter, single blinded RCT of a pilot-tested, nurse-led, mhealth technology-centered, self-management intervention for further testing at primary, secondary and tertiary cadres of healthcare delivery in Ghana for the control of BP among *recent stroke survivors thereby enhancing generalizability of our findings*. The FOA specifically encourages research "*that use pragmatic clinical trial designs*". We have tailored and refined the PINGS intervention based on feedback received from our pilot trial by **removing** the necessity of a Smartphone, a customized App, internet connectivity, and the inconvenience of multiple daily BP checks and reviews by patients and clinicians. We are proposing to test a refined intervention that is simple to use, fit for purpose and maintains the essential components of the PINGS intervention required for efficacy. ***Thirdly***, we will systematically deploy constructs from the *Normalization Process Theory* to identify implementation barriers and facilitators, to understand the implementation context & to select theoretically informed implementation strategies via multi-stakeholder engagement for the PINGS intervention. We will rigorously pursue implementation outcomes such as acceptability, adoption, appropriateness, feasibility, fidelity & implementation cost of the PINGS intervention in the Ghanaian context. *This NINR FOA seeks studies on "dissemination and implementation research focused on self-management"*. ***Fourthly***, PINGS-2 cross-fertilizes the fields of stroke management, nursing, public health, implementation science, and health systems by promoting team science, to target a major public health problem such as stroke, affecting the most resource-constrained regions on the globe. Ultimately, the intervention, if proven effective & implementable, may eventually be exported to other medically underserved populations in LMICs beyond Ghana as a feasible, and scalable model of post-stroke management. The PINGS intervention is therefore a self-management intervention for a chronic condition (hypertension among stroke survivors) aimed at improving well-being, strengthening self-determination and promoting participation of stroke survivors in health care, and preventing illness and complications in accordance with the FOA for this call.

B.12. Implications: The profound disparity between the rapid surge in stroke burden in LMICs and the striking paucity of human resource availability to provide medical care for recent stroke survivors requires innovative task shifting strategies. A clinically-effective PINGS-2 intervention, if scaled, could potentially:

- Reduce stroke morbidity, mortality, and associated costs after stroke in LMICs possibly by improving medication adherence and control of not only hypertension but for other vascular risk factors such as diabetes mellitus, dyslipidemia, and anti-thrombotic prophylactic therapy for stroke survivors;
- Be applicable to CVD risk reduction for patients with other major CVD entities such as congestive heart failure, chronic kidney disease and coronary artery disease. On the other hand, even if PINGS-2 has no effect, pre-planned analyses will allow us to discriminate aspects of the intervention that may have been otherwise effective, as well as understand differences in efficacy and acceptability within our cohort such that more appropriately designed risk prevention studies can be developed in the future. When we have completed this RCT, we plan to make the products from PINGS available to the research and public health community.
- Of note, the National Academy of Medicine endorsed ("*The United States cannot ignore the reality that the health and well-being of other countries affect the health, safety, and economic security of Americans*") investments in global health research that can be of health benefit by extension to Americans, and learnings from PINGS-2 may be instructive for underserved regions of the United States with high stroke rates.

C. PRELIMINARY DATA

C.1. Prelim Data #1: Validated Questionnaire for Verifying Stroke Free Status – Sarfo et al. developed & validated a pictographic version of the Questionnaire for Verifying Stroke Free Status (QVSFS) with superior diagnostic properties including 98% certainty for determining stroke-free status compared with CT scans in 3 languages spoken in West Africa.[119,120] This instrument is apt in settings where investigative tools such as computerized tomography are not available to rule out a diagnosis of stroke routinely.

C.2. Prelim Data #2: Stroke types, severity, and outcomes in Ghana – The largest study on stroke in SSA involving 4000 case-control pairs from Ghana and Nigeria has recently been completed. 64.4% of strokes were

ischemic& 35.6% were hemorrhagic with Hypertension as the most dominant risk factor with a Population Attributable Risk of 90.8% (95% CI:87.9-93.7) which is the highest to be reported in literature.[121]

C.3. Prelim Data #3: Gaps in Risk factor Control after Stroke in Ghana: We analyzed data on 530 stroke survivors seen at a Clinic in Kumasi, Ghana. We found that at baseline 89.8% had hypertension, 23.5% had dyslipidemia and 20.2% had diabetes mellitus.[42] one year after the index stroke: systolic BP levels were not within recommended targets in a third of patients & ii) ~ 2-3 antihypertensive drugs were required by most patients.[43]

C.4. Prelim Data #4: Using Mobile Health to Modify Risk Factors for Stroke Prevention: We performed a meta-analysis of all eligible RCTs that assessed effect of mHealth on stroke risk reduction. Of 79 studies identified, 13 of them met eligibility criteria (6 for glycemic control & 7 for smoking cessation) &were included in the final meta-analysis. There were no eligible studies for dyslipidemia or hypertension. At 6 months, mHealth resulted in greater HbA1c reduction (mean difference of decrease in HbA1c: -0.39%; 95% CI: [-0.74,-0.04], P=.03) & relatively higher smoking abstinence rates (OR: 1.54; 95% CI: [1.24, 1.90], P<0.0001). While it seems that mHealth improves glycemic control & smoking abstinence rates, there is a need for mHealth to be tested in modifying the premier vascular risk factor, i.e. hypertension, specifically in people with or at risk of stroke.[122]

C.5. Prelim Data #5: Attitudes of Stroke Patients to mHealth for BP Control and Med Adherence in Ghana: We used a concurrent triangulation design to collect quantitative and qualitative data from stroke survivors, caregivers, community leaders, clinicians, and hospital personnel to explore the barriers, facilitators, and perceptions toward mHealth related to hypertension management among post-stroke survivors in Ghana.[123] 99.5% (n=200) of survey participants expressed a willingness to participate in a research study involving mHealth and the majority (96.5%) thought it would be worthwhile to conduct studies on how mobile phone or computers could help with control of blood pressure in the community. **Three-quarters (76%) of participants had access to a mobile phone with internet capabilities**.

C.6. Prelim Data #6: mHealth-based Med Adherence and BP Control in Ghanaian Stroke Patients: In a pilot RCT,[44,45] we evaluated the feasibility of an mHealth technology-enabled, nurse guided intervention in improving BP control among 60 recent Ghanaian stroke survivors; 30 each in the intervention & standard of care (SC) arms. Participants in the intervention arm received a Blue-toothed UA-767Plus BT BP device & smart phone for monitoring, reporting BP measurements & med intake under nurse guidance for 3 months vs. SC. Tailored motivational text messages were delivered based upon levels of adherence to the medication intake. To control for attention exposure, the SC arm received SMS messages dealing with healthy lifestyle behaviors but not with med adherence. The PINGS intervention was stopped after month 3 & both groups were followed up until month 9. Primary outcome measure was BP control (<140/90mmHg at month 9). Secondary outcome measures included: (i) medication adherence measured using the Medication possession ratio (MPR) at month 9 and (ii) technological glitches. Outcomes: (1) *BP control* at month 3 by Intention to treat analysis was 20/30 (66.7%) vs 14/30 (46.7%), p=0.12 in the intervention and control arms respectively at interim analysis at end of intervention.[44] At month 9, proportion on the intervention vs. controls with systolic BP<140mmHg was 22/30(73.3%) versus 13/30(43.3%), p=0.035 in favor of the PINGS intervention.[45] (2) *Medication possession ratio* scores at month 3 were better in the intervention arm (0.88 ± 0.40) vs. SC (0.64 ± 0.45) arm (p=0.03), & at month 9 was (0.95 ± 0.16) vs (0.98 ± 0.24), p=0.56. **These pilot trial findings support testing an mHealth intervention aimed at improving BP control after stroke in an under-resourced region.[44,45] We observed a potential signal of efficacy with the intervention, which we have refined further to test within a larger definitive clinical trial in the current proposal**.

D. SOLID COLLABORATIVE RESEARCH TEAM

Our interdisciplinary team has been involved in several projects of direct relevance to PINGS-2 research focus. Our interdisciplinary team represents experts in medicine, nursing, public health, health communication, and information technology. (see bios).

D.1. Principal Investigator: Bruce Ovbiagele, MD: is Professor and Associate Dean at the University of California, San Francisco with experience in the development and implementation of interventions targeted at stroke risk reduction in vulnerable populations.[3,124-131] His team at UCSF leads a chronic care model-based intervention to improve post-stroke outcomes (NCT01900756) in Nigeria,[132] PINGS-1, a nurse-guided mHealth pilot project to assist stroke patients in Ghana (NCT02568137),[89] and PACESETTER a trial of a blue-toothed electronic medication tray to improve stroke outcomes in South Carolina (MD012441). Dr. Ovbiagele has authored several articles on optimal BP control & stroke outcomes,[133-142] and major expert management guidelines.[3] Of note, he is the Editor-in-Chief of *eNeurologicalSci* (eNS), a peer-reviewed journal of the World Federation of Neurology (WFN) and former Chair of the International Stroke Conference (ISC), the premier scientific stroke meeting in the world.

D.2. Multiple Principal Investigator: Fred Stephen Sarfo, MD, PhD, PhD: is a consultant neurologist and a double PhD holder in molecular medicine and epidemiology with expertise in the conduct of RCTs at the Kwame Nkrumah University of Science & Technology (KNUST). 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[26-28] and PINGS[44,45,89] feasibility RCT on mHealth interventions to improve blood pressure control among stroke survivors in Kumasi, Ghana. He is also currently serving as the PI for a multi-center study involving 6 sites in Ghana (rural, semi-urban and urban sites) involved in prospectively evaluating outcomes of hypertension and diabetes mellitus among 3,300 recruited patients being followed by 18 months.[143-146] Dr. Sarfo has the requisite scientific training, experience and a working local knowledge of the Ghanaian health system[147-156] to coordinate & implement the PINGS-2 trial as MPI.

D.3. Senior Key Personnel: Albert Akpalu, MD: is a neurologist at the University of Ghana at the capital city in Accra. He is the Head of the first Stroke Unit in Ghana with recognition in a special world report in the Lancet.[46] He has been a Co-I along with Prof. Ovbiagele, and Sarfo on the SIREN study.

D.4. Other local Investigators: John Amuasi, MD, PhD: is a member of faculty at the Global Health department of the School of Public Health, KNUST with a PhD in Health research & policy. His research focus is on improving health systems, services and outcomes through implementation research in LMICs.[157-160] **Dr. Samuel Blay Nguah, MD, MSc (Biostatistician):** is a pediatric cardiologist and biostatistician serving as a biostatistician for trials conducted at KNUST, Ghana. [161,162]

D.5. Preparatory work at Study Sites: A PINGS Task Force (PTF), created to guide implementation strategies, consists of the overall PIs, Senior Personnel, Site PIs, information technologist, biostatisticians and Public Health experts. The PTF will review intervention design, recommend local adaptations, assess implementation, and trouble shoot challenges. Review of evidence regarding effectiveness of planning approaches and patient, provider, and health system interventions to improve chronic CVD care in resource-limited settings in Ghana revealed that intervention features with consistently positive effects included cultural tailoring, one-on-one interactions with individualized assessment incorporating treatment algorithms, focusing on behavior-related tasks, providing feedback, & high-intensity interventions delivered over a long duration (≥6 months). We will also constitute an **Implementation Strategy Committee** including representatives from the Ghana Health Ministry, Food and Drugs Authority, National Health Insurance, Hospital administrators from the study sites, Clinicians (nurses and physicians from participating study sites, Stroke survivors and lay community members to help in formulating and co-designing an implementation strategy with the research team to address Specific Aim 3.

E. APPROACH

E.1. Overview: The overall objective of **P**hone-based **I**ntervention under **N**urse **G**uidance after **S**troke II *(PINGS-2)* is to deploy a hybrid study design to firstly, demonstrate the efficacy of a theoretical-model-based, mHealth technology-centered, nurse-led, multi-level integrated approach to substantially improve longer term BP control among 500 recent stroke patients encountered at 10 hospitals in Ghana.[46] Secondly, PINGS II seeks to develop an implementation strategy for routine integration and policy adoption of mhealth for post-stroke BP control in a LMIC setting. *We will leverage experience gained from the NIH Global Brain Disorders funded R21 pilot study (NS094033) to test efficacy of a refined, culturally-tailored, and potentially implementable intervention aimed at addressing the premier modifiable risk for stroke & other key variables in an under-resourced system burdened by suboptimal care & outcomes.*

E.2. Settings: PINGS-2 will be conducted at 10 sites in Ghana comprising of 2 academic/tertiary medical systems which serve urban populations, 4 secondary level and 4 primary level medical centers for peri-urban & rural populations, in Ghana (Table 1). Each of the 10 participating sites encounters sufficient volumes of stroke patients and can meet expected recruitment target over the project lifespan. The 10 sites serve an estimated population of 12 million Ghanaians. *The inclusion of lower cadres of healthcare in Ghana is to allow us to test the intervention among socio-economically deprived stroke patients.*

Table 1. ***PINGS-2 Participating Sites and expected Recruitment targets over 4 years for PINGS Trial***

Site (Hospitals)	Recruitment target	Description
Korle Bu Teaching Hospital (KBTH)	125	This is a 1,500 bed tertiary hospital serving as the main referral hospital of the southern part of Ghana, and of the capital Accra. KBTH admits up to 800 stroke patients yearly with mortality rate of 22% and has a dedicated stroke clinic run by a multi-disciplinary team of neurologists, stroke nurses, physiotherapists, nutritionist, and occupational therapists. CT-scan for validating stroke is available on site.
Komfo Anokye Teaching Hospital (KATH)	125	This is the second-largest hospital in Ghana and a tertiary level health institution in the Ashanti Region. It is the main referral hospital for the middle to northern belt of Ghana. It is the teaching hospital affiliated to the medical school in Kumasi. Stroke also forms a major cause of admission with up to 700 admissions yearly and with mortality of up to 30%. The center has CT and MRI scans.

Cape Coast Regional Hospital (CCRH)	50	This is a secondary level hospital situated in Cape Coast in the Central region of Ghana. The facility has 200 beds and has 6 Physician Specialists who manage an average of 300 stroke cases a year. The centre has a CT scan and runs Specialist Medical Out-Patient clinics for stroke survivors. CCRH also has a vibrant Accidents & Emergency Department for triaging acute stroke cases.
Agogo Presbyterian Hospital	50	This is a secondary level hospital situated in the Ashanti region in the Middle belt of Ghana. It is affiliated with the Agogo Presbyterian University. The facility has 200 beds and has 2 Physician Specialists who manage an average of 200 stroke cases a year.
Atua Government Hospital	25	Atua Government hospital is a secondary level hospital situated in the Southern belt of Ghana in the Eastern Region of Ghana. The facility has 75 beds and 4 experienced Medical Officers involved in the management of an average of 100 stroke cases yearly.
Kumasi South Hospital	25	Kumasi South hospital is a secondary level hospital situated in the Ashanti of Ghana in the Ashanti Region of Ghana. The facility has 80 beds and 4 experienced Medical Officers involved in the management of an average of 50 stroke cases yearly.
Obuasi Government Hospital	25	Obuasi Government Hospital is a government primary level hospital situated in Obuasi, a gold mining town. The facility has 65 beds and 8 experienced Medical Officers involved in the management of an average of 60 stroke cases yearly.
Manhyia District Hospital	25	Manhyia District Hospital is a government, primary level hospital situated in Kumasi in the Ashanti Region of Ghana. The facility has 80 beds and 4 experienced Medical Officers involved in the management of an average of 50 stroke cases yearly.
Ankaase Methodist Hospital	25	Ankaase Methodist hospital is a primary level in the Afigya Kwabre District in the Ashanti Region of Ghana. The facility has 50 beds and 3 experienced Medical Officers involved in the management of an average of 100 stroke cases yearly.
Tafo Government Hospital	25	Tafo Government hospital is a primary level hospital situated in the Ashanti Region of Ghana. The facility has 80 beds and 4 experienced Medical Officers involved in the management of an average of 45 stroke cases yearly.

E.3. Guiding Frameworks: Lack of theoretical development has been proposed as a major contributor to failure to demonstrate efficacy of complex interventions in preventive care after stroke.[163] As such, we anticipate that an effective intervention to improve outcomes among stroke patients in LMICs must be based in solid theoretical constructs *tailored and relevant to* the unique health care situation. The PINGS-2 conceptual model integrates key theoretical constructs and is the framework for organizing the intervention components.

Table 2. PINGS-2 Theoretical Frameworks/Models

Model/Theory	Description	Justification
Transtheoretical	• Behavioral interventions are most effective for people at the "determination" or "action" stage.[164,165]	• An intervention in the context of a recent stroke is likely to motivate individuals to be ready to change
Self Determination Theory (SDT)	• Competence & autonomous regulation are critical components. Building sustained motivation in SDT involves development of autonomous regulation, fostered by inculcating a sense of ownership & meaning in one's behavior changes consistent with personal values, beliefs or life goals.[166]	• Confidence to engage in desired behaviors is increased when motivation is high. Behaviors are more likely to be sustained than those resulting from controlled motivation via external (e.g., "doctor's orders") or negative internal (e.g., shame, guilt) pressures.[167]
People, Activity, Context & Technology	• Users must feel at ease with and perceive the technology as helpful in reaching desired goal.[168, 169]	• Obtaining input from patients, caregivers, and providers in development of tailored culturally sensitive motivational messages needs to be pertinent to the patients and their circumstances
Chronic Care Model (CCM)	• Identifies the essential elements of a health care system that promote high-quality chronic disease care • PINGS-2 intervention will comprise CCM components of **delivery system redesign** (*home BP monitoring, increased follow-up visits, phone text/audio messages*), **self-management support** (*patient education, dedicated phone texts*), and **community resources** (guidelines, support groups, local information).	• Majority of interventions based on model improved care processes or outcome measures, and reduce health care costs.[73] • Delivery system redesign (enhanced care coordination) component of model linked to improvements in outcomes.[74-77] • Self-management support (confidence in one's ability to behave in a way to produce a desirable outcome) component of model has been strongly linked to favorable outcomes.[74, 78,79] • Multiple components of the CCM may influence care.

E.4. PINGS-2 (Specific Aims 1 and 2)

- Aim 1: To demonstrate the efficacy/effectiveness of the PINGS intervention vs. usual care in achieving improved BP control at 12 months as primary outcome measure among recent stroke survivors receiving care at 10 medical centers (at primary, secondary and tertiary-levels care) in Ghana in a randomized controlled trial.
- Aim 2: To preliminarily assess the effectiveness of the PINGS intervention vs. usual care at improving self-management, medication adherence, quality of life, as well as a reduction in subsequent CVD related re-hospitalizations, & major adverse cardiovascular events as secondary outcomes.

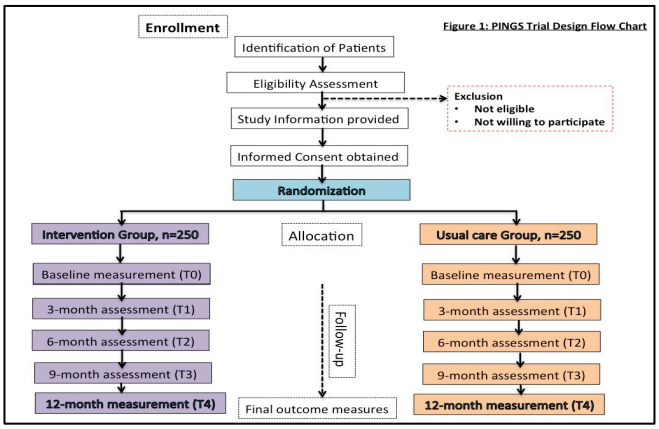
E.4.1. Design: PINGS-2 is a phase III randomized, open label, blinded endpoint clinical trial to evaluate the efficacy and acceptability of a nurse-led, mHealth technology-centered, multi-level integrated approach in achieving sustained BP control among recent stroke survivors with hypertension encountered at primary, secondary and tertiary medical centers in Ghana, a LMIC in SSA compared with usual care. This is a 2-arm RCT involving 500 stroke survivors with individual participant randomization.

E.4.2. Eligibility: *Inclusion* – (i) age ≥ 18 years (stroke is commoner above this age cut-off); (ii) male or females (sex is a biologic variable of interest); (iii) recent stroke (within one month of symptom onset)- stroke may be ischemic or hemorrhagic based on brain imaging or diagnosed clinically using the locally validated version of the 8-item questionnaire for verifying stroke free status (8-QVSFS) when neuroimaging is not feasible[119]; (iv) uncontrolled HTN (SBP ≥ 140 mmHg at both the last clinical encounter post-stroke and the eligibility screening visit) - SBP is used as the selection variable since most African hypertensives <60 years have systolic or combination systolic/ diastolic HTN and for most patients, controlling SBP also results in DBP control;[170-172] (v) patients *or family carers* should own a basic mobile phone that can receive text/audio messages.

Exclusion – Any condition that would limit participation in follow up assessments, such as severe cognitive impairment/dementia (MMSE ≤24).

E.4.3. Training of Physicians and Nurse navigators on Standard of care for post-stroke vascular risk factor management using expert consensus guidelines: Physicians and nurse navigators at all 10 study sites will receive an initiation and annual training sessions on standard practices for post-stroke vascular risk factor management using local & current international guidelines[170] to be delivered by Dr. Sarfo (MPI) to minimize variability in provider practices across study sites and enhance patient safety.

E.4.4. Recruitment: The proposed procedures have been feasible to implement among non-English speaking patients in the pilot trial conducted in Ghana.[44,45] All communications/evaluation will in the participant's preferred language, mostly Akan, Ga or Ewe which are the dominant languages spoken at the proposed study sites. Patients encountered in the neurology clinics, general medicine clinics and more broadly out-patient clinics of participating hospital sites with a diagnosis of stroke will be eligible for recruitment into the PINGS II trial. This is to ensure we enroll stroke survivors from the various points of orthodox medical service delivery in the country for representativeness and generalizability of study findings. Leaders at each of the participating hospitals have committed to support recruitment for the proposed study (see letters). Standardized recruitment tools and procedures will be used at each site. The site research coordinators (RC) will ensure that all inpatient and outpatient clinic lists collated daily. He/she will meet with and review this list with their site PIs to confirm patient's potential eligibility. Following confirmation of likely eligibility, the RC will contact, then schedule eligible patients for a screening visit for eligibility confirmation and obtain informed consent from patient or valid proxy after detailed explanation in a native language the patient understands. *Fulfillment of eligibility criteria will be confirmed by a site study or site PI.* See Figure 1 for PINGS study design flow chart. Participants whose SBP average ≥140 mmHg from the last 2 readings of 10 min protocol at the eligibility screening visit will have height, weight, and waist circumference measured. The enrollment questionnaires will then be administered by the Research Assistants (Table 3).



E.4.5. The Intervention Protocol: The proposed PINGS intervention was developed based on preliminary data & practical experience including the published experiences of the PINGS investigative team from UCSF & KNUST in Ghana. This on-going relationship between the 2 Universities has been productively nurtured over the past 5 years of collaborative research experience. *Caregivers/ family members will be encouraged to participate in all aspects of the intervention because they can provide self-management support & are often instrumental in ensuring adherence to medication regimens and lifestyle habits*.

E.4.5.1. Patient Level interventions: The patient-level intervention is based on the principles of **shared decision making**, a process in which clinicians & patients work together to make decisions & select tests, treatments & care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values.[173] The **main components of the patient-level intervention** are (i) domiciliary blood pressure self-monitoring, (ii) use of phone alerts to set medication reminders, and (iii) patient education on hypertension, cardiovascular risk management and stroke. The patient-level intervention will be delivered over the 12-months of follow-up.

- ***Home BP monitoring***: All patients in the intervention (called PINGSTERS) will be provided automated blood pressure monitors (Omron version 10). The nurse navigators will show the patient and/or their family caregiver how to use BP monitor to take 3 consecutive BPs using a 10 min protocol. PINGSTERs/family caregiver will demonstrate ability to measure BP following the protocol before leaving the clinic. ***Dose of intervention***: Patients will be encouraged to take their BP at least once a week. Participants will be shown that BP readings <140/90mmHg on antihypertensive treatment is optimal. However, if BP exceeds thresholds (e.g., BP>180/105 or <100/75 mmHg) during a session, they should call the **nurse navigator** for advice.
- ***Medication reminders using phone alerts:*** At the beginning of the intervention, the physician for the patient and the nurse navigator will meet to review each patient's prescribed treatment plan including antihypertensive medications. The nurse navigator and PINGSTER patient will establish times antihypertensive medications and other medications (such as statins, anti-platelets, and so forth) will be taken daily. They will receive oral & written information on times when meds should be taken. An alert will be set on the PINGSTERs/caregivers' own phone to go off daily at the times prescribed medications should be taken

to serve as a reminder. Adherence to medications will be assessed using pill counts and calculation of Medication Possession Ratios during scheduled clinic visits.

- ***Patient education on hypertension, cardiovascular risk reduction & stroke:*** PINGSTERs will receive audio and text messages delivered in the preferred local dialect once a week on HTN/stroke facts and importance of medication adherence. Sample of messages include "reducing the intake of salt, eating vegetables& fruits will help keep your blood pressure controlled". The SMS text and/or audio messages on HTN/stroke are intended to improve health literacy on stroke and its risk factors. SMS messages will be sent in English language, *however for participants who cannot read or speak English, audio messages in their preferred native language will be sent instead*. The mHealth intervention in PINGS II will be delivered by Viamo Technologies Limited®. Viamo is a local Ghanaian company with presence in 22 countries specializes in using mHealth technology to drive behavior change in LMICs. Viamo will use SMS and local-language interactive voice response (IVR) messages using in-house algorithms to disseminate hypertension behavior change messages and medication reminders to participants on **basic feature phones** with the objective of increasing self-efficacy. (see letter of support).

E.4.5.2. Provider Level: Providers will follow care protocols based on expert consensus practice guidelines to address HTN management. A task-shifting strategy using nurse navigators will be used in this study to deliver primary care to stroke patients with HTN. Male and female nurse navigators will be recruited and trained for this study. The Nurse navigators will receive approximately 80 hours of intensive training over a 2 week period prior to initiating study at each study site. They will participate in didactic and group-based learning on the fundamentals of non-communicable diseases, health promotion/disease prevention and patient centered communication. They will receive instructions on how to reinforce patient adherence to antihypertensive regimens through patient- and family-centered approaches & also receive training on proper BP measurement technique. If a PINGster's mean BP exceeds thresholds (e.g., BP >180/ 105 or <100/75 mmHg), the patient will contact the **nurse navigator** via a phone call or text message for advise on what to do. The nurse navigator will follow an algorithm to address issues relating to non-adherence, side effects, insufficient dosing of antihypertensive med, and so forth. In instances where a clinic visit is required to address BP threshold breeches or health related issues, the nurse navigator will arrange with the research team to have patient seen.

E.4.6. Usual care Protocol: Inclusion criteria include owning a cell phone with at least SMS and voicemail. To control for attention exposure, they will get SMS messages dealing with healthy lifestyle behaviors (smoking, diet, physical activity) but not with med adherence, HTN or stroke related issues. Similar to the intervention group, the usual care patient will have a total of 5 follow-up study visits during which various study outcomes (see Figure 1) will be assessed. Usual care participants will also be contacted by phone monthly to confirm contact information and to inquire about hospitalizations.

E.4.7. Health care access during and after intervention: Both during and after the intervention, study participants will be followed up at the study sites at scheduled visits for evaluation of study outcomes and have access to the study physicians for *unscheduled visits for any health urgencies or emergencies, in particular where BP breeches require hospitalization for urgent management*.

E.4.8. Outcome and Mediator Measures: Primary outcome is proportion of participants with BP<140/90mmHg at 12-months which is the major modifiable step to stroke event rate reduction. We will also conduct longitudinal comparisons of systolic BP in the intervention vs. usual care groups over the course of follow-up evaluations. Participants will be given an appointment encounter solely for collecting evaluation data at the times listed in Figure 1. Trained assessors with no contact to the PINGS study team will perform all study measurements. Potential mediator/moderators of risk factor control and implementation outcomes will also be collected.

E.4.8.1. Physiological/Laboratory Measures

i. BP measurements: Three readings will be taken by trained study coordinators using an automated BP monitor with the patient seated comfortably for 5 min prior to the measurements, following guidelines.[174,175] Average of the last 2 BP readings will be used as the measure for each visit. Uncontrolled BP is defined as average clinic systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mmHg per guidelines.[176]

E.4.8.2. Self-report Measures and Other Information: Self-report measure outcomes will be assessed using validated questionnaires (see Table 3) administered by trained Research Assistants blinded to allocation of study participants to record responses of participants.

Table 3. PINGS-2 Outcomes and Mediators

Outcomes	Brief Description
Systolic Blood Pressure (Primary outcome)	Target goal of <140/90 mmHg measured at baseline, months 3, 6, 9 and 12. Measured by blinded evaluator using an automated BP monitor.

Self-management (Secondary outcome)	Compared between the two groups using the validated Hypertension Self-care Profile questionnaire (HBP SCP) with items that compositely assesses behavior, motivation and self-efficacy of hypertension management. Assessed at months 4, 8 and 12 (α.83-.93, r = .64) [181]
Medication adherence (Secondary outcome)	Measured using Medication possession ratio[177] and 14-item Hill-Bone compliance (HBC) to high blood pressure therapy scale with items that assess medication adherence, clinic appointments and salt intake[178] assessed at months 3, 6, 9 and 12 (α.76-.83, r = .64) [179,180] MPR and HBC will be measured in both PINGS and usual care arms at stated time points.
Cardiovascular ED encounters and re-hospitalizations (Secondary outcome)	To be assessed via *once monthly calls* to patients and/or carers over 12 months of follow up in both the PINGS and usual care groups. Patient carers in both arms will also be encouraged to contact study team within 48 hours of hospitalizations for prompt and blinded adjudicat of all potential CVD ED encounters to minimize reporting bias between the two groups.
Major Adverse Cardiovascular Events (Secondary outcome)	Major Adverse Cardiovascular events (MACE) to be assessed include recurrent stroke: fatal/ severely disabling stroke or non-fatal stroke; Co Disease: Acute STEMI/NSTEMI, sudden cardiac deaths. MACE will be confirmed by a blinded adjudicator by reviewing where available clinical notes supported by investigations e.g. CT scan, EKGs, review of death certificates or verbal autopsy if death occurs outside hospital.
Health Literacy in HPT/stroke (Mediator)	Self-Report: HTN/stroke Knowledge questionnaire (r=.70),[182,183] Health literacy questionnaire (r = .74, .82),[184,185] Assessed at months 0, 6,12.
Health-related quality of Life (secondary	The EQ-5D questionnaire,[186] will assess state of health of study participants at baseline and Month 12.
Disability/Functional status (Mediator)	Functional status after stroke will be assessed by Research Assistants using the Modified Rankin Scale[187,188] with a scores ranging from 0 to 6, where 0=no functional limitation and 6 = death. Assessed at months 0, 3, 6, 9 and 12.
Sex, Age, cultural, socio-economic Factors, study site (mediator)	Assessed based on self reports at baseline. Cultural factors to assess include language spoken at home, religious observances, acceptance of gender roles; occupation, religious beliefs and dietary practices.
Side effects, Adverse events	As reported by participants during follow-up using NCBI toxicity criteria

E.4.8.3. PINGS Intervention Implementation Outcomes: Among the 250 subjects assigned to the PINGS intervention, we will use surveys, qualitative or semi-structured interviews, checklists to assess **six (6)** implementation outcomes proposed by Proctor et al[189] namely (i) **acceptability** (satisfaction with content, complexity, comfort, delivery and credibility of PINGS); (ii) **adoption** (uptake, utilization, intention to try, refusal rates); (iii) **appropriateness** (perceived fit, relevance, compatibility, usefulness); (iv) **feasibility** (suitability for everyday use, practicability); (v) **fidelity** (use checklist to assess whether PINGS was delivered as intended, quality of program delivery); (vi) **Implementation cost** (marginal costs of the intervention & delivery strategy). Furthermore, among providers across the 10 study sites, we will assess provider satisfaction level (e.g. assess provider fatigue from breaches in BP thresholds) using Healthcare provider satisfaction questionnaire.[190]

E.4.9. Statistical Considerations

E.4.9.1. Randomization: Once eligibility, consent & baseline data are confirmed, participants will be randomly assigned to PINGS intervention vs. usual care in a 1:1 allocation ratio, stratified by study site. An adaptive block randomization scheme will be developed & maintained by the lead study biostatistician. Once a patient is randomized he or she will be entered into the study and included in intent-to-treat analysis. The randomization assignment will be known to the project coordinator, and the statistician in charge of the randomization procedure, but not known to the research assistant who will be conducting participant follow-up assessments.

E.4.9.2. Power and Sample Justification: Our sample size calculation and power analyses are based on the proportion with BP<140/90mmHg at 12 months, the premier modifiable risk factor for stroke. In a recent pilot study[44,45] by this group in Ghana, where this proposed study will take place, 60 subjects (30 per group) were randomized to PINGS & control arms with BP<140/90 mmHg at month 9 was 46% versus 40% after withdrawing the PINGS intervention after 3 months.[45] We anticipate at least 60% BP control rate in the intervention arm (lasting for 12 months) versus 44% control in the usual care arm, using a type I error of 0.05, a power of 90%, & a two-sided test, we need at total of 406 subjects. Assuming 20% loss to follow up, the conservative target for enrollment is 500. We conservatively expect ~50% will not meet eligibility criteria or may decline to participate, so we can potentially recruit over 500 patients from ~ 5,550 stroke patients encountered at 10 hospitals over 4 years.

E.4.10. Data Management and Analysis

E.4.10.1. Analysis: Descriptive statistics will be computed for all study variables, including average follow-up time, retention rate, protocol deviations and violations, and will be compared by treatment group. We will use t-test (Wilcoxon rank sum test) for continuous variables and chi-square test for categorical variables to make comparisons between two groups. The primary analysis will be performed according to the principle of intention to treat. However, we will also do per-protocol sensitivity analysis. All outcomes will be modeled using regression analyses adjusted for baseline factors that show imbalance after randomization and compared to analysis that does not adjust for residual baseline differences.[192,193] A nominal p value of 0.05 or less will be considered as statistically significant in the primary analysis. A linear mixed model with the 12-month outcomes as dependent variable and baseline value as a covariate will be used to test the hypotheses in Aims 1 and 2 adjusting for other baseline covariates that show imbalance. Assessment of the fit of the models will be made using residual and diagnostic plots. We will employ longitudinal data methods (generalized linear mixed models [GLMM]),[194] which account for correlation of outcomes due to repeated measurements & missing at random (MAR) data to study the change in outcomes over time between the two groups. We will model binary (logit link& binomial distribution) and count outcomes (log link and poisson or negative binomial

distribution) by properly selecting the link and distribution option of the GLMM. In addition, to evaluate sensitivity of study conclusions to missing data, we will use both last value carried forward& multiple imputation methods to estimate single end-point outcome measures and carry out analyses on the complete data set. We will also use the MNAR statement in SAS 9.4 to make sensitivity analysis on the MAR assumption. If we suspect violation of MAR then we will report the most plausible sensitivity analysis results.[195] Trajectory of BP and other related outcomes will be modeled via GLMM. Differences in time to recurrent events between the two groups will be compared using a log-rank test & a Cox proportional hazards (PH) model (we will test for the PH assumption) will be used to adjust for observed confounders& for clustering via frailty models. Additional analyses will assess patients' adherence to intervention and ***biological variables, in particular, age of participants, sex (male versus female), cultural, socio-economic and family factors on primary and secondary outcomes such as self-management, medication adherence outcomes***. We will adjust self-reported measures for potential measurement error using standard techniques.[196]

E.4.10.2. Management: Data will be captured via REDCap (a free, secure, web-based application) and overseen by a data management and analysis team comprising statisticians at KNUST. Data will be reviewed on a bimonthly basis and issues will be communicated to the project coordinators for prompt resolution.

E.5. Data Safety Monitoring Board (DSMB): We will utilize a DSMB comprised of three experienced external experts (see letters), who will meet twice per year to review the study progress, safety, ethics, and outcomes.

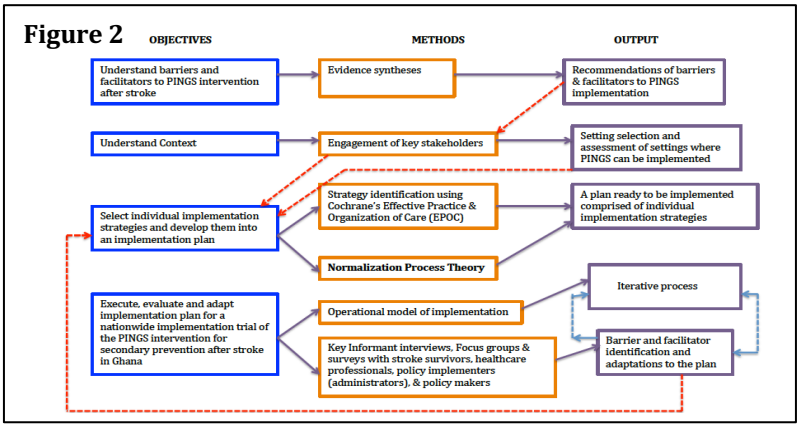
E.6. PINGS-2 (Specific Aim 3)

Aim 3: To identify context-specific implementation facilitators and barriers, to understand the implementation context, and craft a theoretically-guided and evidence-based implementation strategies for routine use and policy adoption of the PINGS intervention in Ghana through multiple stakeholder engagements.

E.6.1 Study Design: Guided by the Normalization Process Theory (NPT), Community-based participatory research (CBPR) and NIH best practices for mixed methods research, we will conduct a mixed methods study to identify implementation barriers and facilitators, understand the implementation context and propose theory- or framework-guided implementation strategies for the PINGS intervention.

E.6.2. Theoretical underpinnings of PINGS Implementation strategy in Ghana: A greater use of explicit theory in order to understand barriers and facilitators, select implementation strategies and design interventions, has been advocated to advance implementation research.[118,197] The Normalization Process Theory (NPT) is a widely used[198,199] theory of implementation that explains the process by which an intervention becomes, or indeed fails to become, normalized into routine practice.[200,201] NPT is represented by four constructs namely *coherence* (the work that people do to understand and make sense of a practice), *cognitive participation (*the work that people do to engage and support a new practice), *collective action (*the work that people do to enact a new practice, and make it workable and integrate it in its context), *and reflexive monitoring (*the work that people do to reflect on and evaluate enacting a new practice in context). We will also be draw on principles derived from the work by Grol and Wensing[202] to provide a systematic approach to implementation planning for the PINGS intervention.

Figure 2



E.6.3. Description of research plan to accomplish study aim 3 (refer to Figure 2): The PINGS Implementation Strategy Committee with representation from the Ghana Health Ministry, National Health Insurance, Local IT consultants, Hospital administrators, Clinicians (nurses and physicians from participating study sites, Stroke survivors and lay community members will be key stakeholders working with the PINGS taskforce in crafting an implementation strategy for the PINGS intervention in Ghana for specific aim 3.

E.6.3.1. Understanding the barriers & facilitators for implementation of PINGS: The Research team will undertake a systematic literature review on factors that influence the implementation of evidence-based mHealth based, self-management interventions for secondary prevention of CVDs after stroke in LMIC settings. Data from the review will be extracted and synthesized according to a Framework for Implementation (the Consolidated Framework for Implementation Research[203]) which categorizes implementation factors as relating to the intervention; the inner& outer contexts; the individual; or the process of implementation.

E.6.3.2. To develop a thorough understanding of the implementation context: To understand the context for

implementation of PINGS intervention into routine care in Ghana, we will engage key stakeholders including policy makers, implementers, Health providers at various cadres of service delivery & stroke survivors and family caregivers as end-users of the PINGS intervention. We will employ implementation methods such as *concept mapping*[204] *and group model building*[205] *which are inherently participatory approaches* with the potential of galvanizing stakeholders around common goals and creating consensus on implementation barriers.

E.6.3.3. To select theoretically informed and evidence based implementation strategies for PINGS: We will identify potential strategies from the Cochrane Effective Practice and Organization of Care (EPOC) taxonomy of implementation strategies.[203] The evidence synthesis and assessment of the implementation context will inform the selection of the most suitable strategies to implement the PINGS intervention. Our selection of implementation strategies will be guided by the Normalization Process Theory, choosing strategies that would bring about change based on increasing coherence, cognitive participation, collective action and reflexive monitoring and its sub-domains. For each barrier identified at the patient, provider, health-system, and policy-level, we will propose implementation strategies following guidelines proposed by Proctor et al[118].

E.6.3.4. Execution, evaluation and making adaptations to the implementation plan: The implementation strategies identified will be used to refine aspects of our proposed study before enrollment of study participants. We will perform assessments of acceptability, feasibility, fidelity and appropriateness of the PINGS intervention during the trial. Periodic meetings (twice each year) will be scheduled by the Implementation committee to discuss progress, trouble shoot challenges identified and co-create solutions.

E.6.4. Procedures: We will conduct **7 FGs (n=45-60 participants)** followed by **20 KIIs.** The FGs will last 60-90 minutes & the KIIs will last approximately 45-60 minutes & will occur at a location convenient to participants. A trained moderator will conduct the sessions with another member of the investigative team taking field notes during the session. Written consent will be obtained from participants prior to the start of any session. The purposive sample (based on demographics of the stroke survivors assigned to the PINGS intervention) for the FGs & KIIs (based on the clinical care providers (MDs, nurses, pharmacists, hospital administrators, policy makers) will be recruited through snowball techniques. **Survey data** will also be collected through self-filled questionnaires to be completed by stroke survivors on PINGS intervention (n=30) & healthcare workers involved in post-stroke care (n=20 from primary, secondary & tertiary medical facilities), health administrators & policy makers (n=10) after obtaining informed consent.

E.6.5. Data management and analyses: All FGs and KIIs will be digitally recorded and transcribed verbatim for qualitative analysis. All data will be uploaded and stored on REDCap, a secure data storage system. Transcripts of the audiotapes and field notes from the de-identified KIIs and FGs will be used for data analysis. The transcripts will be imported into the text analysis software (i.e. NVIVO[206]) for data management, & thematic analysis by the qualitative analyst. For the initial analysis of the data, the investigators will listen to the audio recordings and review the transcripts. The 'Framework Analysis' approach[207] to be used includes five key stages: familiarization, identifying a thematic framework, indexing, charting, mapping, & interpretation. The investigative team will share findings by a process known as member checking[208] with at least three FG and KII participants.

E.7. Training, Fidelity, and Compliance

E.7.1. Training: We will conduct training workshops for study coordinators and PINGS-2 providers at the beginning of the study. The workshop will be on study protocol, instruction in obtaining informed consent, filling out data collection forms, BP measurement, tasks and responsibilities of the study staff, education protocols, and patient flow. This training will consist of 3 full days in Year 1, and to prevent decay of skills, follow-up training sessions will be conducted every 12 months. The PINGS Task Force and the relevant study partners will provide oversight and ongoing supervision of training/coaching sessions, as well as random fidelity checks. To support fidelity of implementation, we will develop a comprehensive training manual (with step by step activities for implementation), provide orientation, training and return demonstration of procedures, and ongoing monitoring with checklist of steps (at least quarterly) with additional training as needed to support fidelity of implementation in both the health care and patient settings.

E.7.2. Patient Adherence with Protocol: Strategies to help ensure optimal levels of adherence include: (1) Stressing importance of attending all study visits; (2) Requesting names and telephone numbers of three friends and/or relatives who know how to reach the patient in the event we lose contact. *Several components of the PINGS interventions will also be administered in the preferred native language to enhance adherence*.

E.8. Anticipated Problems & Proposed solutions

E.8.1. Participant Accrual and Retention: We have chosen a one year primary time point to balance maximizing study follow up with studying a clinically useful time period of adherence. Multiple tactics will be used to facilitate high patient retention including obtaining full contact information for patients, caregivers, and relatives (e.g. identifiers of

location of residence for contact tracing, telephone numbers of patients and caregivers) at time of enrollment and updating every 3 months. Transportation will be provided for clinic visits.

E.8.2. Individual Randomization: We are randomizing patients instead of clusters, because it is the most statistically efficient method for showing efficacy & would require the smallest sample size.[209] Cluster randomization is appropriate when contamination threat is high[210] but we believe contamination threat is minimal given that the Home BP monitor, protocol-based phone calls to nurse navigators, & educational audio messages will apply to the intervention group with a very low probability of the usual care group having access to all 3 components of the PINGS intervention.

E.9. Work Plan and Timetable: PINGS-2 is expected to last a total of 4.5 years from initiation of the first study site to completion of the last clinical trial participant. Activities in the first 9 months of Year 1 will include development of a detailed manual of operations, obtaining IRB and Ghana Foods and Drugs Authority approvals for the study protocol, setting up logistics, formation of a Data Safety Monitoring Board, development of a data management system, and training of study coordinators and nurses.

E.9.1. Pre-trial pilot testing of modified PINGS intervention: We will run a small pilot to pre-test the PINGS intervention among ≈10 stroke survivors (1 from each study site) for 1-month trial to trouble-shoot the intervention & make further modifications if required before starting the main trial by month 9 in year 1.

E.9.2. Recruitment & Follow-up of PINGS study: Anticipated *monthly* recruitment rate is ~1 participant (from each of 6 primary-level centers), 2 participants (from each of 2 secondary-level centers), up to 4 participants (at each of 2 tertiary-level centers) over 36 months will provide an estimated 648 participants (greater than 500 in the proposed study) for the clinical trial. Trial enrollment will be staggered by center, starting with two centers at a time, and for all centers initial recruitment targets for first few months lower than average targets to enable study sites get used to the trial processes and incorporate the study into their center. Recruitment will be stopped once the planned number of RCT participants is attained per site. The implementation strategy aims will start from year 1 through to year 5 to capture the change process during implementation. Data cleaning, final data analyses and manuscript preparation will take place in Months 54-60.

Table 4. Schedule of Activities

Activities	YEAR 1				YEAR 2				YEAR 3				YEAR 4				YEAR 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Ethics approval and renewal	X				X				X				X				X			
PINGS Task Force & Implementation Committee meetings	X	X			X		X		X		X		X		X		X		X	
Hire, orient, train project staff	X	X	X																	
Pre-testing of PINGS intervention		X	X																	
Subject recruitment & follow-up				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Implementation Science Studies				X				X				X			X		X	X	X	
Study Annual meetings			X				X				X				X				X	
Project Coordination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reports, manuscripts		X		X		X		X		X		X		X		X		X		X