Program to Avoid Cerebrovascular Events through Systematic Electronic Tracking and Tailoring of an Eminent Risk-factor (PACESETTER)

ClinicalTrials: NCT03401489

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jenkinsc

MUSC-CON [Company address]

RESEARCH STRATEGY

B. SIGNIFICANCE AND INNOVATION

B.1. Burden of Stroke

Stroke is a major contributor to death, disability, and dementia. [1-4] Beyond the personal toll, costs (e.g. direct expenditures and lost productivity) related to stroke are prohibitive.[44] About 25% of strokes are repeat occurrences, and recurrent stroke leads to further functional decline and subsequent mortality.[45-49] Patients who are readmitted vs. not readmitted within 30 days of discharge are significantly more likely to die within 30 days of discharge after re-admission (13% vs. 10%) and within the first year of discharge after readmission (43% vs. 24%).[50] Causes of first rehospitalization within 30 days after stroke are cerebrovascular disease (14.9%), cardiovascular disease (14.0%), and noncardiovascular disease (71.2%).[50]

B.2. Regional, Racial, Rural disparities in Stroke

Recent United States (US) population-based data show that while there has been a decrease in stroke incidence among Non-Hispanic Whites (NHW), the incidence of stroke among African Americans (AA) has remained virtually the same. [5] This is especially worrisome since a higher stroke incidence and mortality among blacks (vs. NHW) has been present for several decades. [6-10] This racial disparity is even more prominent in the Southeastern region of the US, where 3 states have long been recognized as representing the 'buckle' of a 'stroke belt'. [9,14,15] One of these 3 states is South Carolina (SC),[16] where our proposed study will take place. Adding to the sense of urgency is a projected future widening of stroke prevalence in the US for race-ethnic minorities than NHWs. [17] In addition, poorer access to emergency stroke care and stroke rehabilitation in rural vs. urban areas of the Southeast have been reported,[11,12] there is a 1.45× higher prevalence of stroke in rural vs. urban areas,[51] higher stroke mortality rates in rural vs. urban areas,[13] and since 2004 within the Southeastern US, the rural-urban stroke disparity seems to be increasing.[52] SC is in the top third of US States by proportion of people residing in rural areas (http://www.dailyyonder.com/how-rural-are-states/2012/04/03/3847/).

B.3. Ameliorating the Burden of Stroke

Stroke (including recurrent stroke) is highly preventable via risk factor control,[53,54] By far the most powerful modifiable stroke risk factor is hypertension (HTN),[55,56] and uncontrolled HTN after a stroke is a major predictor of recurrent stroke.[45-49,57] 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.[58],[19] However, less than one third of recent stroke survivors have BP controlled ≥ 75% of the time. [19] Therefore, optimal blood pressure (BP) reduction needs to be at the center of any serious effort to lessen the burden of stroke in nation's stroke buckle, and is a major focus for this application.

B.4. Barriers to HTN Control after Stroke

Multiple strategies for treatment in stroke populations have demonstrated meager utilization rates in several studies and trials. The typical stroke patient is likely 1) older with deep-seated routines and habits and 2) has associated co-morbidities that require polypharmacy (and control of blood pressure alone may require 3 separate prescriptions). Thus, the combination of the need for dedicated follow-up and the chronicity of post-stroke treatment is an inherent wellspring for fragmented and costly healthcare. Hence, the need for more streamlined communication continues to be urgent. Presented with such a reality, healthcare providers must continue to pursue newer methods for increased accessibility and information exchange between themselves and patients. So although sustained adherence to HTN medications can control HTN and reduce stroke events,[59-61] lack of adherence is a leading modifiable barrier to BP control.[20,21,23,62] 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. No BP control RCT to improve outcomes among US stroke survivors has used real time medication reminder tactics & BP self-monitoring guided by behavioral change theory.

B.5. Solutions to HTN Control after Stroke

Developing a culture of preventive health care is imperative for the future for health care delivery, particularly in underserved regions like many areas in the Stroke Buckle. 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.[63] Therefore, encounters between patients and their health care professionals become a critical intersection for information exchange, decision-making and motivation.[64] 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.[65] 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. [66-72] *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.[71,72] Self-BP measurement improves patient compliance with antihypertensive therapy,[73] and a systematic review of self-management programs among patients with diabetes, asthma, and HTN found improvements in relevant physiologic outcomes.[72]

B.6. Mobile Health

Efficacious, feasible and sustainable BP control programs after stroke are needed. [58] 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 permits optimal medication adherence guided by the patients' physiological data. [33,36] This technology is relatively inexpensive and provides real-time feedback to boost patient self-efficacy. Automated summary reports of patients' adherence and BP can be uploaded to providers' networks, helping mitigate clinical inertia by reducing regimen alteration time. [33,36]

B.7. Innovation

This proposal is innovative because of the following elements: ***First***, it cross-fertilizes the fields of stroke management, information technology, psychology and health systems, to target a major public health problem such as stroke, affecting the most disenfranchised. ***Second***, this study applies synergistic constructs of self-determination theory of competence (akin to self-efficacy) and autonomous regulation (sustained internally driven motivation)], as well as technology-based personally designed automated reports with direct user involvement, combined with evidence from current expert consensus clinical practice management guidelines. ***Third***, from an implementation science perspective, **P**rogram to **A**void **C**erebrovascular **E**vents through **S**ystematic **E**lectronic **T**racking and **T**ailoring of an **E**minent **R**isk-factor *(PACESETTER)* aims to assess the incorporation of its stroke intervention into all 3 safety net/academic health sytems in a given US state especially burdened by stroke, thereby enhancing knowledge about the complexity of stroke interventions, and especially the nature of the challenges encountered in low resource settings and for populations traditionally underrepresented in research. Altogether, the **intervention, if proven implementable and effective, may eventually be exported to other medically underserved populations in the US beyond SC as a feasible model of post-stroke management**.

B.8. Implications

A clinically-effective PACESETTER intervention, if scaled, could potentially: a) reduce stroke morbidity, mortality, and associated costs after stroke in the stroke buckle and US, b) be applicable to CVD risk reduction for patients with other major CVD entities such as coronary artery disease, congestive heart failure and chronic kidney disease, and c) bridge racial, regional, and rural disparities in stroke outcomes. PACESETTER will be assessed at the three key tertiary healthcare system in the entire state of South Carolina. These geographically dispered hospitals (Figure 1) are all affiliated with universities supported by the State Government and serve as Safety Net facilities for the poor and underserved including race-ethnic minorities and rural dwellers. As such a positive outcome will likely have the buy-in of healthcare policy makers at all levels in the State, thereby increasing the chances of sustainability of the intervention in routine clinical practice beyond the period of study funding. On the other hand, even if PACESETTER 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 PACESETTER available to the research and public health community.

Figure 1. Map of South Carolina

C. PRELIMINARY DATA

C.1. Prelim Data #1: *Using Mobile Health to modify risk factors for stroke prevention*

We searched PubMed from January 1, 2000 to May 17, 2016 using keywords: mobile health, mHealth, short message, cellular phone, mobile phone, stroke prevention and control, diabetes mellitus, hypertension, hyperlipidemia and smoking cessation. We performed a meta-analysis of all eligible randomized control clinical trials that assessed the effect of mHealth. Of 79 studies identified, 13 of them met eligibility criteria (6 for glycemic control and 7 for smoking cessation) and 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) and relatively higher smoking abstinence rates (OR: 1.54; 95% CI: [1.24, 1.90], P<0.0001). We conclude that mHealth improves glycemic control and smoking abstinence rates, two factors that may lead to better stroke outcomes, but 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. This review and meta-analysis will be presented at an upcoming stroke conference.

C.2. Prelim Data #2: *Impact of Electronic Pill Tray Devices*

Electronic devices like the Vaica pill tray (Vaica Medical, Inc.;Tel Aviv Israel; Healthcom Inc., Sullivan ,IL; United States distributor) which will be used in PACESETTER, have been shown helpful among patients intent on taking their medications but are either forgetful or only modestly motivated.[74] Indirect electronic monitoring methods have been shown to reflect actual intake in such individuals and do not artificically increase adherence.[74] A review of 37 medication adherence electronic device trials (32 RCTs, 5 nonrandomized) involved 14 chronic conditions including hypertension.[75] Compared to control groups, programs that provided solely reminder signals with or without additional feedback related to pill intake failed to show greater improvements in medication adherence. Programs which integrated electronic device data with health related feedback from providers showed greater improvements than control groups (84.8 vs. 68.4%). Our earlier studies involving Black hypertensive patients included these components and all resulted in high acceptability, usability, improved adherence, and BP control.[41,76-78]

C.3. Prelim Data #3: *Attitudes of Stroke Patients to mHealth Monitoring to support BP Control and Med Adherence*

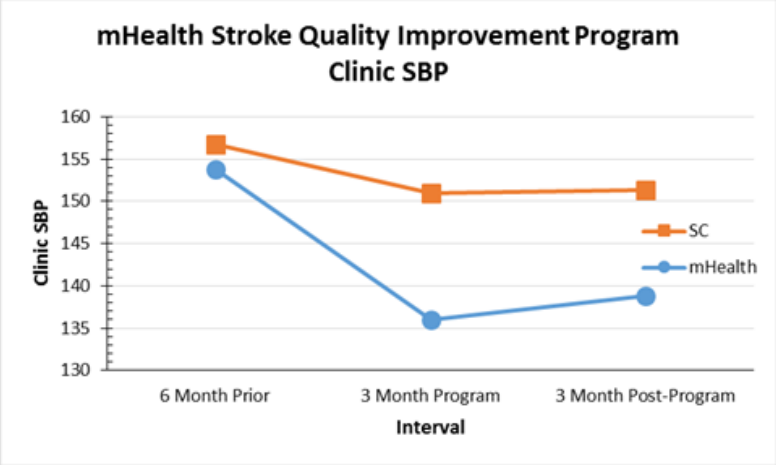
Between June 2013 and July 2014, 60 patients completed surveys to evaluate attitudes toward mHealth technology for chronic disease management during a stroke clinic visit.[39] Mean age of participants was 57 years, female (59%), White (55%), and had more than a high school education (54%). Almost half of the sixty (41.67%) reported some difficulty with daily medication adherence with 28.3% forgetting to take their medications, and 25% reported missing $\geq$ 1 day of prescribed pills within the last two weeks. 7% endorsed stopping medications while asymptomatic or "feeling fine." 65% used home BP monitors, and 53.3% used some version of a medication dispensing device at home. An overwhelming majority (93.3%) owned a working mobile device, 35% owned a smartphone, and > 75% sent or received text messages on their phone. Over half (53.3%) belong to households with at least one person owning a smartphone. Participants demonstrated substantial access to computers with > 70% with a working computer in the home. 78.3% reported using mobile devices for text, 35% email, 43.3% for internet use, and 45% used the devices with other software applications. Over 75% of participants would use a mHealth system if the device(s) were provided free of charge. A majority of patients checked "agree or strongly agree" to all questions evaluating their willingness and confidence in mHealth as alternative means of delivery for health communication. 71.7% were willing to use a free "smart" device as directed if given assistance. 85% were comfortable with a nurse or doctor monitoring health information using mHealth. 78.3% believed mHealth would help them with medication adherence, specifically following doctor's directions. 71.7% believed private health information would be protected via mHealth technology. Finally, 83.3% were confident this technology would be a means of effective communication between themselves and respective health providers. No statistically significant differences in attitudes towards mHealth were observed in this sample based upon race, income, medication adherence, use of smartphones or BP devices/medication boxes. When comparing participants based on whether they would or would not use a mHealth system, the majority (52%) of those who reported they would use the mHealth system had a household income of less than $30,000, compared to 44% in the group that would not use the device (p=.01).[39]

C.4. Prelim Data #4: *Pilot Study of mHealth Medication Adherence and BP Control in Recent Stroke Patients*

We evaluated the feasibility and preliminary signals of clinical outcomes of a mHealth medication and BP self-management system for recent ischemic stroke patients with uncontrolled hypertension encountered at MUSC.[42] A smartphone enabled medication adherence and BP self-management system,[40,41] was adapted for utilization by stroke patients using a patient and provider based design. A 3-month pilot quality improvement initiative was conducted in 24 hypertensive post-stroke patients. Eight patients were randomly selected to receive the mHealth program involving a GSM enabled electronic medication tray; a wireless Bluetooth enabled BP monitor (A&D model UA-767PlusBT San Jose, CA, USA); and a 4G smartphone (if needed) that received and transmitted encrypted physiological data and delivered text message reminders to measure BP. Culturally-attuned motivational and reinforcement text messages were sent based upon medication adherence rates. [40,41] Following instruction on usage of the devices, the patient/participant (and in 2 cases, a caregiver) were required to provide a successful demonstration before completion of their visit, and then to use the monitor for measurement of BP and the medication tray for their medications . Primary care providers received weekly summary reports of mHealth patients' medication adherence and BP readings. Patients were sent text messages every 3 days to measure BP in the

morning and evening using the A&D device using a standardized resting BP protocol.[40,41] BP readings were automatically sent via Bluetooth to the mobile phone and from there, through cellular network encrypted, to the secure and Health Insurance Portability and Accountability Act compliant data repository. No patient names were transmitted and no identifying information was stored on the smartphone. Participants received immediate audio and visual feedback via smartphone on average BPs after each measurement; and the application charted cumulative averages over time against threshold lines for BP control (i.e., set at <140/90 mmHg). [79] A weekly email report, tailored to the treating physician's guidelines, summarized the patient's adherence to medication dosing and BP monitoring, and BP data (i.e., average, range, % within recommended guideline classifications).[79] The treating physician made medical regimen changes as warranted, and the program coordinator was notified via email. The changes were duplicated in the programming of the medication tray after the coordinator established with the patient that the changes had been enacted. All patients received standard care (SC) at the hospital's stroke clinic, which included visits roughly every 6 weeks depending on the medical indication and time since index stroke. The mHealth group used the system for 3 months. Clinic BP readings and record of emergency department (ED) use were retrieved from patients' electronic medical records from the 6 months prior to the stroke, the 3 month period during the mHealth program, and the subsequent 3 months. Large reductions in clinic systolic BP were observed for mHealth group compared to the SC group (Figure 2). Mean systolic BP at baseline was 153.9 (standard deviation [SD]: 11.4) in the mHealth group vs. 156.7 (SD:26.5) in the SC group; at program end systolic BP was 136.3 (SD: 15.9) in the mHealth group vs. 151.3 (SD: 14.5) in the SC group; and 3 months post-program final systolic BP was 137.8 (SD: 24) in the mHealth group vs. 151.9 (SD: 13) in the SC group. Comparing the 6 month pre-stroke period vs. the 6 month period involving the QI program and followup, the mHealth group showed an 87.5% reduction vs. a 20% reduction in ED use by the SC group. Collectively, these data support the feasibility of using an mHealth medical regimen self management system to improve medication adherence and BP control after stroke.[42]

Figure 2. ***Reductions in clinic SBP were observed for the mHealth group vs. SC group***



C.5. Prelim Data #5: *Acceptability and Usability of the mHealth Intervention in Stroke Patients*

A series of Likert scale questions were completed by the mHealth participants at conclusion of the pilot program mentioned above, which assessed acceptability and usability.[42] Responses ranged from 0 (strongly disagree) to 4(strongly agree). Scores ranged from 3.25-3.75 with average of 3.5. Overall satisfaction with the program was 3.5; program was easy to learn (3.25), easy to use (3.75), and audio/visual BP feedback on the phone and various pill tray alerts were well liked (scores of 3.6). Finally, level of increased involvement in staying healthy and likelihood of recommending to other stroke patients were both rated 3.5.

D. SOLID COLLABORATIVE RESEARCH TEAM

Our interdisciplinary team has been involved in several projects of direct relevance to PACESETTER's research focus and these results/experiences. Our interdisciplinary team represents experts in medicine, health communication, cultural tailoring, nursing, public health, information technology and clinical psychology (see bios). Available protocols, consent forms, and encounter scripts, will be adapted for PACESETTER.

D.1. Principal Investigator: Ashley Wabnitz, MD

Dr. Wabnitz is a Vascular Neurology trained clinician at the Medical University of South Carolina (MUSC) with a strong clinical background as well as an interest in stroke prevention. Following completion of her clinical training, she completed a one year StrokeNet Research Fellowship through which she receive specialized educational opportunities such as dedicated mentorship and online seminars devoted to developing academic clinicians with a particular interest in stroke research. This makes her particularly suited to participate as the PI at MUSC for the PACESETTER grant, which serves to study secondary stroke prevention through analyzing novel methods of outpatient blood pressure management in the post-stroke population.

D.2. Senior Key Personnel: Frank Treiber, PhD

Dr. Treiber is Professor and Director of Technology Applications Center for Healthful Lifestyles at MUSC; a clinical psychologist and expert in community-based clinical trials testing the use of health technology to improve CVD outcomes.[41,76-78] He is PI of 2 NIH R01s

and 1 R21 involving mHealth technology. One RCT (R01HL114957) is investigating use of smart phone delivered meditation to achieve better BP control among Black & White pre-hypertensives. The R21 (HL 118447) is an efficacy RCT evaluating an mHealth strategy called SMASH among Hispanics with uncontrolled HTN. Dr. Treiber has conducted 3 separate feasibility RCTs involving patients with uncontrolled HTN. [99,100] One RCT involved predominantly Black kidney transplant patients with uncontrolled HTN. Subjects were randomly assigned to a smart phone med adherence stops hypertension (SMASH) program or standard care (SC). Participation & retention rates were 75% & 91%, respectively, & the system was safe, highly acceptable, & useful to patients & providers. Compared to the SC group, the mHealth group had significant improvements in medication adherence & reductions in clinic-measured systolic BP. All SMASH subjects exhibited clinic BP control (<140/90 mmHg) at 1 month onward vs. 20% in SC. Providers made more anti-HTN drug adjustments in the mHealth group based on information provided in weekly reports.[41] In another study, among Hispanics with uncontrolled HTN, all SMASHers exhibited BP control at months 1-3 in resting clinic BPs vs. 16.6% of SCs.[101] Drs. Ovbiagele and Treiber are collaborating on one NIH-funded study - PINGS (NCT02568137), [42] and co-authored the publications that form the basis for the preliminary data provided.

D.3. Senior Key Personnel: Carolyn Jenkins, DrPH, FAAN

Dr. Carolyn Jenkins is Professor of Nursing at MUSC, PI for the CDC-funded REACH U.S. South-Eastern African American Center of Excellence for Eliminating Disparities, and an expert in implementing multi-level interventions and focus group research.[102-105] Dr. Jenkins has shown i) that health disparities for Black patients can be decreased/eliminated with changes in community systems, health care, and individual behavior;[104,106-108] and ii) amputations can be significantly reduced (44%) across 2 counties through community-based participatory actions.[109] Drs. Ovbiagele and Jenkins are collaborating on three NIH-funded studies - THRIVES (NCT01900756),[89] SIREN (U01NS079179) and PINGS (NCT02568137), [42] and co-authored the publications that form the basis for preliminary data provided below.

D.4. Senior Key Personnel: Souvik Sen, MD MPH FAHA

Dr. Souvik Sen is Professor and Chair of Neurology at the University of South Carolina School of Medicine in Columbia, SC. He is PI of the NIMHD-funded PeRiodontal treatment to Eliminate Minority InEquality and Rural disparities in Stroke (PREMIERS) study (R01MD009738), which seeks to test whether intensive periodontal treatment reduces the risk of recurrent vascular events among ischemic stroke and TIA survivors. PREMIERS addresses specific issues with regards to recruitment of African-American and rural stroke/TIA patients advocating the use of culturally appropriate strategies to educate the study subjects regarding stroke, periodontal disease and the periodontal stroke link. Both Dr. Ovbiagele and Dr. Sen work as co-investigators of the South Carolina Collaborative Alliance for Stroke Trials (U10NS086490), a unique collaboration between 3 academic medical centers, MUSC, USC, and Greenville Health System with a primary goal of expanding state-wide capacity to conduct high quality stroke research.

D.5. Senior Key Personnel: Bruce Ovbiagele, MD, MSc, FRCP

Dr. Ovbiagele is Associate Dean of the Medical School at the University of California San Francisco and the Chief of Staff at the Veteran's Affairs Hospital. He has experience in the development and implementation of interventions targeted at stroke risk reduction in vulnerable populations.[80-88] Along with a team at the Medical University of South Carolina, he leads a chronic care model-based intervention to improve post-stroke outcomes (NCT01900756) in Nigeria,[89] and a nurse-guided mHealth pilot project to assist stroke patients in Ghana (NCT02568137).[42] Previously, Dr. Ovbiagele led a multi-pronged program to enhance treatment utilization after recent stroke that was associated with high post-discharge adherence rates, achievement of target biomarker goals,[81-83] and fewer recurrent vascular event rates.[83] Dr. Ovbiagele has authored several articles on optimal BP control & stroke outcomes,[90-98] and major expert management guidelines.[88] Of note Dr. Ovbiagele was the Vice Chair of the writing panel for the current American Stroke Association Secondary Stroke Prevention Guideline,[79] and recently served as a member of the Writing Committee for the upcoming American Heart Association/American College of Cardiology Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults, which will be published shortly.

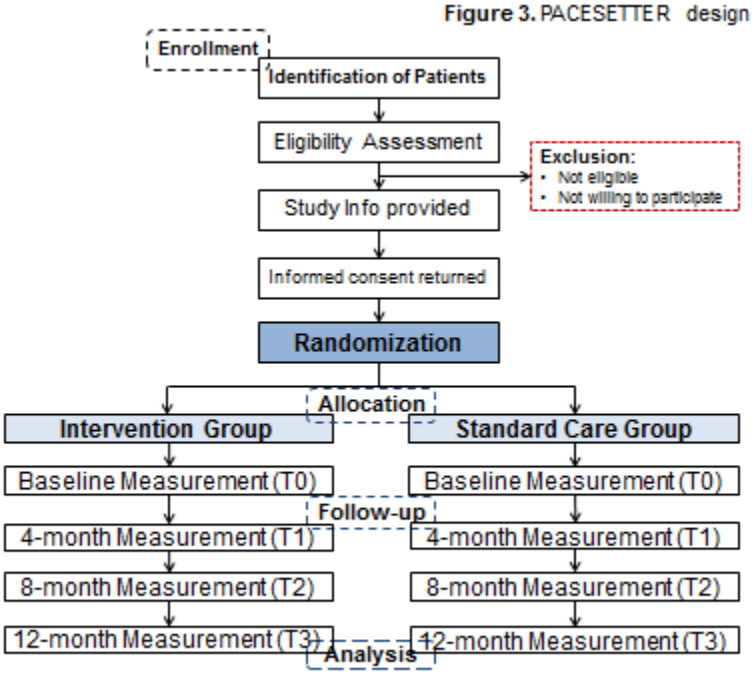
D.6. Preparatory work at Study Sites

A PACESETTER Task Force (PTF) has been created to guide implementation of the strategies. It consists of the overall PI, Senior Personnel, Site PIs, information technologist, and biostatisticians (see appendix for letters of support). The PTF will review intervention design, recommend local adaptations, assess rate of 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 among socially disadvantaged populations revealed that intervention features with consistently positive effects included cultural tailoring, one-on-one interactions with individualized assessment and reassessment incorporating treatment algorithms, focusing on behavior-related tasks, providing feedback, and high-intensity interventions delivered over a long duration (≥6 months).[110]

E. APPROACH

E.1. Overview

Figure 3. PACESETTER design flowchart



The overarching goal of PACESETTER is to determine whether implementation of a one-year theory-driven, mHealth-based intervention will result in significantly better BP control among 200 stroke patients encountered at two of the three safety net sites in South Carolina. We will test (see Figure 3) the efficacy of the intervention vs. standard care in achieving target goals for BP, explore effect on CVD events, and examine provider effects.

E.2. Settings

The two of the three academic/tertiary safety net medical systems in the state of South Carolina (table 1) will be participating in this study, each of which encounters high volumes of stroke patients emanating from surrounding regions and throughout the state.

Table 1. *PACESETTER Participating Sites*

Study Site	City	2015 Stroke Discharges	2015 Stroke Clinic Patients	% African American	Site PI
Medical University of South Carolina (MUSC)	Charleston	1233	655	48 -51%	Dr. Wabnitz
University of South Carolina/Palmetto Health System	Columbia	1300	400	50-52%	Dr. Sen
Regional Medical Center	Orangeburg	243	0	60-68%	Dr. Trivedi

E.3. Guiding Frameworks

Lack of theoretical development (i.e., lack of a conceptually integrated rational for doing a particular thing) has been proposed as a major contributor to failure to demonstrate efficacy of complex interventions in preventive care after stroke.[111] As such, we anticipate that an effective intervention to improve outcomes among stroke patients in SC must be based in solid theoretical constructs *tailored and relevant to* the unique health care situation. The PACESETTER conceptual model integrates key theoretical constructs and is the framework for organizing the intervention components.

Table 2. PACESETTER Theoretical Frameworks/Models

Model/Theory	Description	Justification
Transtheoretical	• Behavioral interventions are most effective for people at the "determination" or "action" stage.[112,113]	• 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.[114]	• 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.[115]
People, Activity, Context & Technology	• Users must feel at ease with and perceive the technology as helpful in reaching desired goal.[116,117]	• 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	• Majority of interventions based on model improved care processes or outcome measures, and reduce health care costs.[66]

	• PACESETTER intervention will comprise CCM components of **delivery system redesign** (*home BP monitoring, increased follow-up visits, phone text messages*), **self-management support** (*patient education, dedicated phone texts*), and **community resources** (guidelines, support groups, local information).	• Delivery system redesign (enhanced coordination of care) component of model strongly linked to improvements in health outcomes. [67-70] • 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.[67,71,72]

E.5. PACESETTER (Specific Aims 1-3)

- Aim 1: To conduct an implementation trial (at the patient level) of the PACESETTER intervention [health technology (personalized phone text messaging and home BP monitoring)] vs. usual care in 200 recent stroke patients with HTN recruited across two of the three main safety net hospitals in the state of SC. Primary outcome is achievement of guideline-recommended systolic BP control at 12 months.
- Aim 2: To explore whether implementation of the PACESETTER intervention vs. standard care is associated with a reduction in cardiovascular event-related emergency department encounters and re-hospitalizations within 12 months.
- Aim 3: To explore whether implementation of the PACESETTER intervention vs. usual care shows a signal of potential efficacy in reducing actual vascular events (stroke, myocardial infarction and death from vascular causes).

E.5.1. Eligibility

Inclusion - Age ≥ 18 years up to 80 years, African American or non-hispanic white, history of stroke (within 3.5 years of symptom onset) and uncontrolled HTN (SBP ≥ 130 at the last clinical encounter post-stroke prior to recruitment) as recorded in the medical record. The participant will also need to own a smartphone with a data plan, and be able to take their own BP and self administer medications, and high risk transient ischemic attack (TIA) as defined by ABCD2 score > or equal to 4 . *Exclusion* – Any condition that would limit participation in follow up assessments, severe global disability (modified Rankin Score ≥ 3), BMI of > 40 kg/m^2, and not being able to speak, hear, or understand English. Patients' medical records will be accessed in order to determine eligibility. If a patient's modified Rankin Score is not available on the medical record, then the measure will be administered after obtaining consent.

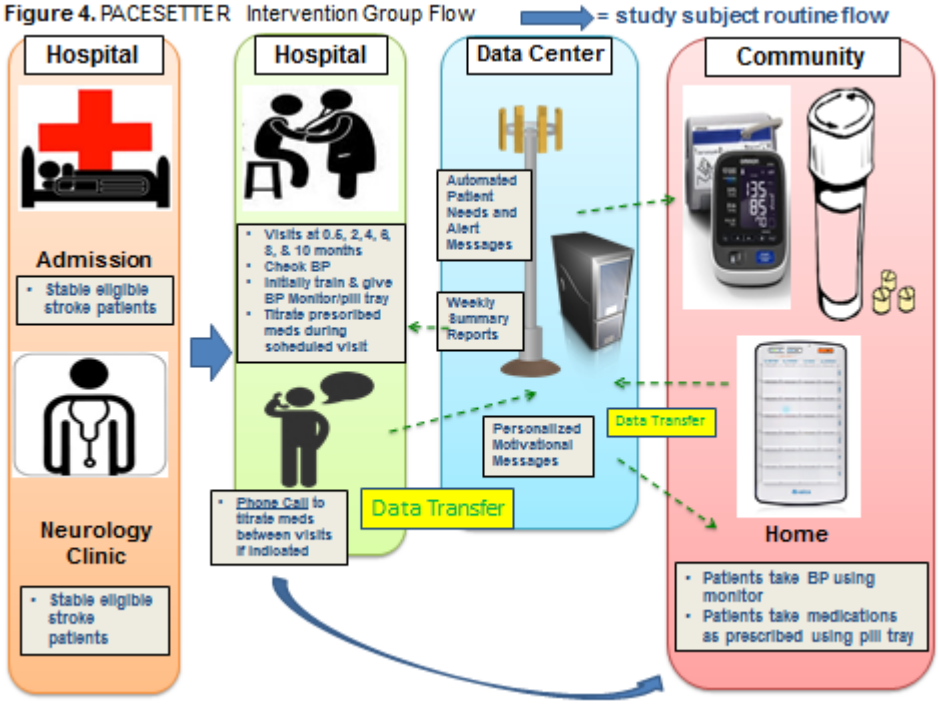
Confirmation of Eligibility

In order to screen for eligibility in person at the neurology clinic, study staff will request to take a series of three blood pressures on the right arm of potential participants, similar to how they are taken in the clinic for the standard of care. Study staff will provide an information sheet for potential participantss explaining the rationale behind taking the blood pressure measurements, how they relate to post-stroke medical regimens, as well as how their measurement taken in clinic by study staff will not be recorded alongside personal health identifiers. The study team will record blood pressure reading in the person's research record (not the medical record). Should the blood pressure reading make the prospective participant eligible for the study, the study team will continue with an explanation of the study and go over the consent documents to check for the prospective participant's willingness to participate and understanding of the study risk and benefits

E.5.2. Recruitment

Proposed procedures have been successful in previous projects among race-ethnic minority patients in under-resourced settings.[101,118-121] Only patients encountered in the neurology wards and clinics of participating hospital sites with a diagnosis of stroke will be eligible for recruitment into PACESETTER. 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 study staff will ensure that all inpatient and outpatient clinic lists and summaries are routinely collated daily and reviewed for eligibility. He/she may meet with and review this list with their respective site PIs to confirm patient eligibility if there are concerns. These data are generated daily and can be readily accessed. Following confirmation of eligibility, study staff will contact, then schedule eligible patients for screening/recruitment, and obtain informed consent (Electronic consent via Doxy.me and remote consenting are also available). Using the IRB approved methods of recruitment, a potential patient that is recruited will be contacted by phone and can be consented via Doxy.me electronic consent . If the patient is interested after using the call script to inform them of the study, we will either move into ICF and HIPAA review or schedule a different time for the patient and study team member to discuss the informed consent and HIPAA. After reviewing of the ICF and HIPAA, the patient will sign and date on Doxy.me. If the patient does not have electronic consenting capability, remote consenting will be done. The consent and HIPAA will be mailed, emailed, or faxed to the patient. Once received by the patient, study staff will call the patient on the phone to discuss the ICF and HIPAA forms and inquire if the patient has any questions while both individuals have the forms in front of them. Once the patient has had sufficient time to review the forms and ask questions, they can then return the signed and dated forms to study staff. The study staff will also sign and date the form and then send a fully executed copy back to the patient. This process will be documented on the documentation of consent process form. If not already completed as part of standard of

care, we will complete serial blood pressures in order to finalize eligibility for the study. These serial blood pressures will be used as the baseline measurements for the study if the average systolic blood pressure is 130 or greater. If the patient has eligible blood pressures, randomization to a study arm will then take place. Randomization lists for each site stratified by race (Black and White) will be prepared by the statistician and randomization will be performed as soon as eligibility and consent is confirmed. See Figure 4 for PACESETTER flow chart. Height weight and mid-arm circumference measured. A set of questionnaires will be administered (see Table 3). If the patient is consented and is unable to be seen in person, the SBP will be confirmed either verbally over the telephone while the patient performs the BP protocol, visually via televisit, or visually with a text message sent to study staff from patient. If the patient does not have a cuff at home, study staff will: 1) coordinate with home health to have blood pressures taken, 2) use bp measurements from the most recent clinic in person appointment, or 3) direct the patient to the closest pharmacy with a bp cuff that they can use to take a bp with study staff on the phone. If bp is not able to be obtained, the patient will not be eligible for this study. Wrist cuffs are acceptable for enrollment BP measurements. Height, weight and mid-arm circumference will be confirmed verbally from patient (if possible) or the most recent medical record data will be used. Patients will complete various forms showing that they can use the med device, BP monitor, phone and app properly. If the patient cannot sign his or her own name, the patient will make a mark as part of the consent process and a witness will sign the consent document as well.



E.5.3. Intervention Group

The proposed PACESETTER intervention (see Figure 4) was developed based on preliminary data, practical experience and a comprehensive literature review including the published experiences of the PACESETTER investigative team.

E.5.3.1. Patient Level: Patients (termed PACESETTERs) will be given a Viaca electronic pill tray & blue-toothed UA-767Plus BT BP device and the PACESETTER app installed on their smart phone for automatic relay of BP data to our central server (Vaica and BP device can be mailed to patients if patient cannot be seen in person). The electronic monitoring medication device is being used in other NIH funded clinical research and is in clinical dissemination across the USA. Study staff will be trained at each of the sites in how to set up the tray and monitor its use correctly according to the patient's current medical regimen as prescribed by their health care team. The provider and PACESETTER patient will establish the times that meds will be taken daily. The designated pill compartment on the Vaica tray (28 compartments for up to 4 doses/day for 7 days) emits a bright blue blinking light for 30 minutes when it is time to take the meds. If the compartment is not opened and emptied within that time, an intermittent chime ensues for 30 minutes. If the compartment is not opened and emptied during that time period, the subject receives an automated SMS . PACESETTERs will show they can properly load the pill tray, take 3 consecutive BPs using 10 min protocol, & view the feedback chart &/or hear their BP data from that session on their phone. They will receive written and oral information on adherence criteria: i) take meds within a 3 hr window centered on the prescribed dosing time (within 90 min before or 90 min after designated time.); ii) take BP every 3 days in morning & evening. PACESETTERs will be given a brief beliefs, values, & life goals questionnaire. Responses will be used in a tree structured algorithm to generate personalized motivational & reinforcement messages guided by self-determination theory constructs of competence & autonomous regulation.[114,115] These tailored brief SMS or voice mail messages are based on previous day's reported medication adherence levels and BP data every 3 days (for example, " High five! Proactive care is best practice for a healthy and happy life" and "Give yourself a pat on the back! Your med doses were on time! Keep this up so that you'll be able to enjoy fellowship with your friends at church.") Typically during first 2-3 weeks, messages will be tapered to several times per week & cumulative adherence graphs will be sent during the trial unless adherence drops < 90%. After each BP session, PACESETTERs will receive visual & auditory BP feedback on their phone, & can select charts showing

cumulative averages across weeks/months compared to BP control threshold lines. In addition to personalized messages described above, PACESETTERs will receive text messages 2 times per week on HTN/stroke facts, importance of med adherence, and tips on expressing questions/concerns with a physician.

As in our pilot study[39] & other mHealth medication adherence studies, [41,76-78] medication adherence will be calculated using our modification of Russell et al.'s algorithm[122] which considers dose timing in addition to dose taking, especially important when taking meds with especially short half-lives. A dose taken within the 3 hr window results in a full score for that dosing time; a dose taken outside the 3 hr window but within a 6 hr window results in a half score for that dosing time and a missed dose resulted in a score of 0. Each PACESETTER subject receives a score from 0-1.0 per day and scores averaged over the month. We will also calculate medication possession ratios, [123] on all subjects' HTN medications at each followup evaluation.

E.5.3.2. Provider Level: The study will be led by each site's neurologist. Providers will follow standard of care protocols based on expert consensus practice guidelines to address HTN management. These practice guideline protocols are routinely and currently being incorporated into standard of care now. Providers will use the PACESETTER weekly summary reports and patient files to make decisions regarding medication titrations, scheduling of clinic visits, and general patient medical management. Together, the neurologist leadership at each site, as well as the use of the expert consensus practice guidelines, will help prevent inertia in the PACESETTER prevention arm. The PACESETTER patient will have the patient's medication adherence and BP profile information available in graph form or averages across time frames (e.g., previous week, month, etc.).

Figure 5. *Display of blue-toothed UA-767Plus BT BP device synchronizing along with smart phone*

This HIPAA compliant secure server file system will assist in keeping the site PI, designated healthcare team member and study staff updated via alert messages when needed based on patients' status and treatment plans. Subjects' data will be kept separate from any identifiers in MUSC's enterprise firewalled, encrypted, secure, data warehouse RDBMS (relational database management system) server. Their data are linked by an identified random subject ID#. The list with subject ID#s and all data parts are only accessed via an authenticated secure HTTPS access to the PI and biostatistician. The site PI and any designated healthcare provider/study staff identified within the PACESETTER team will also have a list that links a subject's ID# to their name and contact in order to follow-up on notifications of a BP range breach. Based upon care guidelines, ranges of acceptability will be set for the various parameters. If a patient exceeds any of these ranges the site PI or designated healthcare team member will receive automated text/email of a Patient Alert to check patient with ID #>>>. The site PIs, and designated healthcare team members will also receive summary charts of expert consensus BP management guidelines used by us in other studies.[124] PACESETTER site PIs or designated healthcare team members will receive weekly summary reports, using only patient ID #s based upon their preference (eg., email; EHR with email reminder to view it).If a PACESETTER's mean BP exceeds thresholds (default markers BP >180/ 105 or <100/75 mmHg) during a session, the site PI (neurologist) or appropriate designee will receive an alert SMS or email, call the patient, and conduct the BP protocol again. If BP still exceeds thresholds, appropriate follow-up action will be initiated.

E.5.4. Standard Care (SC) Protocol

To control for attention exposure, the control group will get SMS messages dealing with healthy lifestyle behaviors (smoking, diet, physical activity) but not with med adherence, HTN or stroke related issues. Messages will be same frequency & size as PACESETTERS' motivational/ reinforcement messages for medication adherence. Every 3 days (comparable to PACESETTERS BP monitoring) they will receive an automated SMS directing them to a different 2-3 minute video/YouTube™ clips on healthy lifestyles. For those who prefer hard copy material, brochures (esp. novella format) will be mailed across the trial. SC and PACESETTER physicians will receive same expert consensus guideline charts. Patients in this arm of the study will receive usual care as determined by their providers. Usual care after stroke in the region typically involves at least one scheduled follow-up clinic visit after the initial diagnostic encounter with a neurologist, with subsequent care by a neurologist or primary care physician based on need. However, these patients will be encouraged to follow up with their primary care providers for the treatment of their stroke. SC subjects will also be contacted by phone monthly to confirm contact information and to inquire about hospitalizations. If the participant requests information, study staff will

provide/send relevant materials and will be instructed to check with their primary care provider. Similar to the IG, the patient will have a total of 3 follow-up study visits (phone call visits/televisits will be available for patients unable to follow up in person) during which various study outcomes (see Figure 2) will be assessed.

E.5.5. Outcome and Mediator Measures

Primary outcome is systolic BP at 12-months, which is the major modifiable step to stroke event rate reduction. A secondary analysis will examine whether PACESETTER improved systolic BP by a clinically significant amount. Also apart from the 12 month primary outcome, we will also conduct a longitudinal comparisons of systolic BP in IG vs.SC over the course of followup evaluations. Participants will be given an appointment encounter solely for collecting evaluation data at the times listed in Figure 2.Trained assessors blinded to the randomization arm (with no contact with PACESETTER clinical team and instructed not to infer and probe on the intervention) will perform all study measurements. Potential mediator/moderators of risk factor control will also be collected. If a patient endorses severe depressive symptoms, patient will be referred to the appropriate medical professional.

Table 3. PACESETTER Outcomes and Mediators

Outcome Type	Measurements	Assessment Duration	Target Goal	Baseline	4 months	8 months	12 months
Primary	Systolic blood pressure[173,174]	<15 mins	< 130 mmHg	X	X	X	X
Secondary	Cardiovacsular ED encounters and re-hospitalizations	<10 mins	Group differences	X	X	X	X
	Medication adherence[125]	<10 mins	Group differences	X	X	X	X
	Body mass index[126]	<5 mins	Group differences	X	X	X	X
	Self-management[127,128]	<10 mins	Group differences	X	X	X	X
Tertiary	Stroke, Myocardial infarction, Death	<10 mins	Group differences	N/A	X	X	X
Mediators	Age, education, income, depression,[129,130]	<5 mins	Group differences	X	N/A	N/A	N/A
	HTN/stroke Knowledge,[131,132] Health literacy,[133,134] disability, [135,136] and study site	<10 mins	Group differences	X	X	X	X
	Side effects, Adverse events (as reported)	<10 mins	Group differences	X	X	X	X

E.5.5.1. Physiological/Laboratory Measures

i. BP measurements: Three readings will be taken by trained assessors (if patient is unable to be seen in person, trained assessor will confirm the readings are taken correctly by patient either by verbal confirmation of procedures or visually watching the patient complete the BP measurements) using an automated BP monitor with the patient seated comfortably for 5 min prior to the measurements, following guidelines.[137,138] Average of the last two BP readings will be used as the measure for each visit. Uncontrolled BP is defined as average clinic systolic BP ≥ 130 mm Hg or diastolic BP ≥ 90 mmHg per guidelines.[137]

ii. Body Mass Index (BMI): BMI will serve as a measure of weight loss. Height and weight will be measured without shoes using a tape rule and a validated digital scale respectively. All measurements will be recorded to the nearest 0.1 inch and 0.1 lbs (If patient is unable to be seen in person, study staff will confirm height and weight with patient if possible or use most recent data from medical records).

E.5.5.2. Self-report Measures and Other Information

i. Patient demographics: Socio-demographic data will be used to describe the cohort & examine effects of these factors on outcomes.

ii. Cardiovascular (CVD) Emergency department encounters and re-hospitalizations: will be used to compare health system utilization rates during study. CVD encounters will be based on International Classification of Disease, 9th Revision (ICD-9) codes for the primary discharge diagnosis, categorized as either heart disease or cerebrovascular disease hospitalizations. Heart disease hospitalizations will include those for hypertension (ICD codes 401 to 405), acute coronary artery disease (410, 411), chronic coronary artery disease (412 to 414), dysrhythmia (427), and congestive heart failure (428). Cerebrovascular disease (ICD codes 430 to 438). A statistician blinded to study group assignment will assess the occurrence of these encounters in the SC Inpatient Hospital Discharge Database. All hospitals in SC, with the exception of military & federal institutions, are mandated to provide data on every hospitalization, including demographic information, dates & type of hospitalization, & discharge disposition. SC's Office of Research & Statistics collects these data & freely provides investigators with a patient-based hospitalization database. We have experience using this database.[58]

iii. Medication adherence: Adherence to prescribed antihypertensive drugs will be assessed using the Modified Adherence to Refills and Medications Scale. Medication adherence will also be calculated for all subjects using med possession ratios (MPRs),[123] on all HTN meds at each evaluation and an overall MPR score will be calculated. PACESETTER subjects will have their Viaca based monthly medication adherence scores as their primary measure of medication adherence. All participants in the study will also be contacted by the research staff via phone call at months 2, 6, and 10 to ask you to complete a medication count.

iv. Chart extraction: Information extracted from the medical records will include medications and their dosages, biomarker measurements from clinic visits, and medical comorbidities.

E.5.5.3. Vascular Events (Specific Aim 3)

PACESETTER aims to collect any vascular events that take place while a patient is in the trial. This is being done to ensure that all events are captured in a timely fashion without any recollection biases. In order to do this, all participants & families will be urged to contact the RC as soon as any event that might be a CVD event

has occurred. CVD events will include stroke, transient ischemic attack, or an acute coronary syndrome. Participants with potential CVD events will be evaluated by a study physician within 48 hours. If the history or the exam indicates that a stroke might have taken place, all clinical, laboratory & imaging data needed to confirm the event will be obtained by the RC & sent to a blinded physician adjudicator assigned to each site (see letters of support), for independent review. Final reports regarding the event will be sent to primary research site (MUSC) within 15 days. Participants with events will continue to be followed at scheduled intervals. These are study-specific steps the patient or caregiver will be asked to take once the CVD event has been addressed medically-ie, after the condition been treated and stabilized.

E.5.6. Statistical Considerations

E.5.6.1. Randomization

Once eligibility, consent & baseline data are confirmed, participants will be randomly assigned to PACESETTER intervention vs. usual care in a 1:1 allocation ratio, stratified by race (Black and White) & 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.5.6.2. Power and Sample Justification

Our sample size calculation and power analyses are based on a 12 month change in the primary outcome of SBP, the premier modifiable risk factor for stroke. Large meta-analyses of observational and RCTs have found clinical benefit for having a SBP as low as 115 mm Hg. In addition, a large RCT of SBP-lowering for secondary stroke prevention found similar health benefits for persons with baseline HTN and for persons with baseline normotension. Data from MUSC clinic registry showed that the mean SBP for persons with SBP>120mmHg was 154.5 +/-10.3 mmHg. Using a type I error of 0.05, a power of 92%, a robust correlation of 0.8 between baseline and 12-months outcomes, no change in mean SBP in the control arm from baseline to 12 months and a two-sided test, 80 subjects in each treatment arm (or 160 subjects in total) will enable detection of a net decrease of 0.5 standard deviation units (which correspond to difference of 8.8 mm Hg in SBP). This difference of 8.8 mm Hg in SBP between the two treatments is smaller than the 10 mm Hg threshold cited in the guideline, and thus we have sufficient statistical power with the estimated sample size to detect clinical benefit. An alternative outcome measure to SBP is recurrent stroke, but our sample size is not large enough to detect differences in recurrent stroke over 12-months of follow-up. Although we will facilitate the retention of subjects in the RCT as much as possible, the retention rates in disadvantaged populations are likely lower than in other settings. Assuming 20% loss to follow up, the conservative target for enrollment is 200. Data from MUSC indicated that 85% of all the patients at 3 days post-stroke had a SBP > 120. Thus, we conservatively expect ~50% will not meet eligibility criteria or may decline to participate, so we can potentially recruit over 200 patients including half of whom will be African Americans from the 2 sites over 3 years.

E.5.7. Data Management and Analysis

E.5.7.1. 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 for continuous variables and chi-square test for categorical variables to make comparisons between two groups and corresponding ANOVA for more than two groups. The primary analysis will be performed according to the principle of intention to treat. 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.[140,141] A nominal p value of 0.05 or less will be considered as statistically significant in the primary analysis. Analysis of covariance (ANCOVA) will be used to test the hypotheses in Aim 2 adjusting for baseline differences. 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]),[142] which account for correlation of outcomes due to repeated measurements and clustering by site and missing at random (MAR) data to study the change in outcomes over time between the two groups. In addition, to evaluate sensitivity of study conclusions to missing data, we will use multiple imputation methods to estimate single end-point outcome measures and carry out analyses on the complete data set using the MNAR statement in SAS 9.4. If we suspect violation of MAR then we will do additional sensitivity analysis.[143] Trajectory or change over time in 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 and a Cox proportional hazards (PH) model (we will test for the PH assumption) will be used to adjust for observed confounders. Since all participant data will be included in this analysis, participants missing outcome data will be censored at the last follow-up assessment time. Exploratory analyses will also be performed by sub-groups (e.g. age, gender, race) to determine if any differential efficacy exists. If statistically significant differences are found between IG and CG arms, we will conduct regression analyses further adjusted by variables selected based on a combination of clinical judgment and descriptive statistical findings comparing

baseline characteristics between the IG and CG. These adjustments will help describe likely pathways by which the treatment influenced outcome. Additional analyses will assess patients' adherence to intervention and any secondary outcomes. We will adjust self reported measures for potential measurement error using standard techniques.[144]

E.5.7.2. 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 MUSC. Data will be collected and sent electronically in password-encrypted files from the various sites to the team at MUSC. Secondary measures and demographics will be de-identified and sent to MUSC for double entry and comparison. Data will be reviewed on a bimonthly basis and issues will be communicated to the project coordinators. In particular outlying and inconsistent data values, as well as missing data, will be the targets of the data quality review.

E.6. Data Safety Monitoring Board (DSMB):

Given the minimal risk associated with the intervention, we will utilize an internal Data Safety Monitoring Board (DSMB) with the addition of one external member. The member extraneous to the project will be an experienced academic stroke attending neurologist based at an institution outside of South Carolina. The DSMB will meet twice per year to review study progress, e.g., recruitment, retention, drop out as well as possible adverse events.

E.7. PACESETTER (Specific Aim 4)

- Aim 4: To qualitatively explore provider effects of implementing the PACESETTER intervention vs. usual care, on the provider practice setting using focused ethnography. [145,146]

E.7.1. Procedures

a) Further search and review the peer-reviewed literature related to blood pressure control, medication adherence and stroke as well as lay literature available to the communities and b) produce an integrative review[147,148] of the topic, and c) a brief community-focused review that can be used for community education We will then further develop/refine the observation and interview guide to answer the research questions through the focused ethnography process. The content of the interview guide will embrace a social ecological perspective (i.e., provider and patient, family/caregiver, health systems and community factors) and will use focused ethnography (FE)[145,146,149] and Steps 1 and 2 of the 6 SQuID.[150]

E.7.2. Setting, Sample and Sampling Criteria

Follow guidance of Higginbottom and colleagues[146] we will adapt the FE process to the three provider practice and community settings. Initially, three providers and three persons with stroke in the past 6 months from each setting will be selected as initial research participants. Provider and staff, as well as their patients, (using snowball techniques[151] for identification of sample pool and purposive sampling for selection of participants) will be interviewed for additional contributions to the data-gathering process. The sampling process will continue with purposive sampling[152] by site until no new data related to provider effects of PACESETTER are identified (saturation[153]).

E.7.3. Data Collection

Prior to data collection the research team & interviewer(s) will review ethical issues & the FE & interview/observation techniques for the FE key informant interviews (KIIs). A screening/recruitment tool with demographic information will be used to select providers and schedule interviews. The interview/oberservations will be conducted by a member of the investigative team who will take field notes (video and/or audio). Written consent will be obtained from participants prior to start of anyKII. After the provider KII, they will be asked to recommend others who support or are a barrier to their care for the patient. A recruitment form with demographic information will be given to the person who will return the form to study staff via mail or email. Study staff will contact the person to schedule the interview. Patients and caregivers who will be interviewed will also complete a screening/recruitment demographic form after obtaining consent. Interviews will occur at a location convenient to participants or via telephone (as appropriate). Methods developed by Tremblay[154] will guide interview processes. All KIIs [along with field notes and video (as appropriate)] will be recorded & audio transcribed verbatim for qualitative analysis.

E.7.4. Data Management, Analyses and Reporting

All data after the study is completed will be uploaded and stored on REDCap[155], a secure data storage system. De-identified transcripts of the audiotapes and field notes (including video as appropriate) will be used for data analysis. We will review transcriptions with recordings to check for accuracy and authenticity. The transcripts will be imported into the text analysis software (i.e., NVIVO[156]) for data management, and analyses. For the initial analysis of the data, we will listen to the audio recordings and review the transcripts and begin the process of *a) coding for descriptive labels; b) sorting for patterns; c) identification of outliers or negative cases; d) generalizing the constructs and theories; and e) memoing including reflective remarks*[157]. Saturation of data will be determined when no new descriptive labels are identified. The 'Framework Analysis' approach[158] to be used includes five key stages: familiarization, identifying a

thematic framework, indexing, charting, mapping, and interpretation to meet the processes of Steps 1-2 and partially address Step 3 of the 6 SQuID[150]. To maintain and evaluate rigor, reliability and validity issues in qualitative studies are best addressed as trustworthiness, which is dependent on credibility, confirmability, transferability, and dependability[159]. Credibility will be enhanced by persistent observation and prolonged contact with verifying data[159]. Thus, relationships with a sample of participants will be developed over a period of 2-4 months. As new and different theoretical leads are discovered, participants representing the best source of data will be re-interviewed. Getting confirmation from participants at subsequent visits by reviewing and validating the codes and labels assigned to their statements contributes to confirmability, or objectivity[160]. Competing perspectives must be given equal consideration. The audit trail is helpful, but the researcher will be aware of and document personal bias. Personal values and assumptions will be acknowledged in theoretical memos entered with the narrative data. Another criterion of trustworthiness is transferability. Establishing a comprehensive, account of the context makes it possible for other researchers to consider the possibility of transferring generalizations to another context[159]. To facilitate transferability, a wide range of demographic differences in the sample of providers and their contacts will be targeted for recruitment. We will share through a process known as member checking[161] with at least 5 KII participants.

E.8. Training, Fidelity, and Compliance

E.8.1. Training

We will conduct training workshops for study coordinators and PACESETTER 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,[81-83,87] and patient flow. [162] This training will consist of 2 full days in Year 1, and to prevent decay of skills, follow-up training sessions will be conducted every 6 months. The PTF and the relevant study partners will provide oversight and ongoing supervision of training/coaching sessions, as well as random fidelity checks.

E.8.2. Patient Adherence with Protocol

Strategies will 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. These will be updated every three months.

Table 4. PACESETTER Process Evaluation Approach

Component	Definition	Operationalization	Data collection method
Recruitment	Procedures used to approach patients, at the individual and organizational level	Procedures applied within and outside hospitals to recruit patients; Reasons for non-participation	Recruitment plan Recruitment logbook
Reach	Proportion of the intended population that participated in the intervention	Characteristics of patients; Number of patients that completed the intervention or dropped out; Reasons for withdrawal	Socio-demographic questionnaire Server log file Enrollment logbook
Dose delivered (completeness)	Extent to which the intervention is actually delivered to patients and nurses	Implementation of the encounter visit(s) as intended; Functioning of the patient and provider application as intended (e.g., delivery of SMS messages: healthy lifestyle messages for SC group; BP reminder s; motivationa;/reinforcement; weekly summary reports to MDs	Checklist Interviews of patients Interviews of providers Server log file Helpdesk logbook
Dose received (exposure)	Extent to which patients and providers received and used the intervention	Opinion about the ability of patients to understand and implement the intervention; Patients' and providers adherence towards the intervention(eg. Time-stamped analyses when pill compartments opened daily in relation to predesignated times ; time-stamp analyses of BP data received every 3 days ; MDs opening weekly summary reports in either email or EMR file,etc.;). Number of actions providers applied in follow-up of monitored data	Interviews of patients Interviews of providers Server log files
Dose received (satisfaction)	Satisfaction of patients and providers with the intervention.[163,164]	Experienced benefits, burden, and supportiveness of the intervention by patients and providers; Overall opinion of patients and providers; Facilitators and barriers in applying intervention	Interviews of patients Interviews of providers

E.9. Anticipated Problems

E.9.1. Subject 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 IG patient retention including obtaining full contact information for patients, caregivers, and relatives at time of enrollment and updating every 3 months. Follow-up visits will be scheduled, whenever possible, on days subjects already have scheduled clinic visits or plan to visit the city. Research Nexus will be used as an additional location to complete study visits as needed. Phone call visits and televisits will be available if patients are unable to return to in-person visits. We will seek the guidance of PTF regarding all recruitment and retention strategies. Strategies will include regular telephone and mail contacts; in the CG these will not include material regarding stroke-related health care issues. Participants are receiving modest monies ($50 per encounter, an additional $50 for completing all study visits, and $75 upon completion of KII interview) for being in the trial.

E.9.2. Individual Randomization

We are randomizing patients instead of clusters, because it is the most statistically efficient method for showing efficacy and thus would require the smallest sample size. [165] Cluster randomization is appropriate when contamination threat is high, [166] but we believe the contamination threat is relatively small in this study.

E.9.3. Missing Data

Beyond attrition (wholly missing follow up assessments), we anticipate little missing data. Under the assumption of MAR, our analyses approach yields intent-to-treat parameter estimates that are consistent with what would be expected if there were no missing data. We will conduct secondary analyses of all hypotheses using only patients with complete data for comparison to the primary intent-to-treat analyses. The degree to which results differ (vs. not) between these two analyses will be reported. If the results differ, it will not be possible to determine which is "true." Our position will be to emphasize the intent-to-treat results for both substantive and statistical (preservation of randomization) reasons.

E.9.4. Representativeness

Like most stroke trials, we excluded severely disabled patients. However, moderately disabled patients will be encouraged to participate with involvement of their caregiver, so findings from PACESETTER will be applicable to up to 80%,[167] of stroke survivors.

E.9.5. Higher risk cohort

A group of recent stroke patients is likely to be a higher risk group than the typical primary care population. High-risk individuals will be referred to the appropriate specialized care and closely monitored by the research team.

E.10. Work Plan and Timetable

PACESETTER is expected to last a total of 4.5 years from initiation of the first study site to completion of the last clinical trial subject. Activities in the first 6 months of Year 1 will include development of a detailed manual of operations, obtaining IRB approval 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. Anticipated recruitment rate is ~2 subjects per site per month over 36 months for the clinical trial. Trial enrollment will stop once the planned number of RCT subjects is attained. The focused ethnography will be conducted at end of years 1, 2, 3 and 4 to capture the change process during implementation. Data cleaning, final data analyses and manuscript preparation will take place in Months 54-60.

E.11. Ethical Considerations

The research protocol, informed consent forms, and questionnaires will be approved by Institutional Review Boards at all sites. In all study aspects, participants will need to give signed informed consent. Data collection and storage will follow GCP standards to guarantee data safety and confidentiality. Appropriate safety procedures will be implemented during the pilot to guarantee that at-risk participant are correctly monitored and referred to specialized care if necessary.

E.12 Capacity Building

'Locally-grown' scientists are needed to help understand the unique impact that race, culture, and environment have on the burden of cerebrovascular disease in SC and its environs. Well-trained stroke research scientists in the region would be more likely to show a predilection to work on topics or areas related to the unique challenges linked to stroke outcomes in the area. PACESETTER will incorporate talented post-doctoral scholars (nursing, psychology, public health) and stroke fellows at all participating academic institutions to join the research team as trainees as a way to introduce hands-on implementation research exposure early in their careers. Of note, Dr. Ovbiagele is the Editor-in-Chief of *eNeurologicalSci* (eNS), a peer-reviewed journal of the World Federation of Neurology (WFN) and Chair of the International Stroke Conference (ISC), the premier scientific stroke meeting in the world. He has directly mentored 35 post-doctorate scholars and junior faculty members on 150 peer reviewed publications, and is currently a mentor on a NIH career development award (K23AG044434). Early career investigators will be invited to participate in eNS editorial processes, as well submit their research work and engage in the multiple career development activities at ISC and WFN meetings.

E.13 Potential Risks

All precautions with data management and de-identification of records will be taken to protect the privacy of participants; however, as with any research study, there is always some risk of a breach in confidentiality. Additionally, participants may experience some emotional discomfort or anxiety when completing questionnaires about depression/anxiety or while measuring blood pressure. If needed, the study team will contact the correct professional that can provide assistance should a participant endorse symptoms of depression.

You may contact Dr. Ashley Wabnitz 843-792-1090, or email wabnitz@musc.edu