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DOES CARE IN A SPECIALIZED STROKE PREVENTION CLINIC IMPROVE POST-STROKE BLOOD PRESSURE CONTROL: A RANDOMIZED COMPARATIVE EFFECTIVENESS STUDY

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ABSTRACT

Introduction:

Hypertension is a major risk factor for recurrent stroke, and blood pressure (BP) reduction is associated with decreased risk of stroke recurrence. However, many stroke survivors have poorly controlled BP after their initial stroke. The Stroke Transitions Education and Prevention (STEP) Clinic was established to provide a comprehensive approach to stroke risk factor reduction.

Methods and Analysis:

This multi-center randomized comparative effectiveness study was designed to assess the impact of care in the STEP clinic versus usual care on post-stroke BP reduction. Eligible hospitalized patients with ischemic stroke, hemorrhagic stroke, or transient ischemic attack are scheduled for a clinic screening visit within 4 weeks of discharge if they meet baseline inclusion criteria. At the clinic visit, patients who have uncontrolled BP, defined as automated office BP $\geq$ 135/85 mmHg are randomized (1:1) to either the STEP clinic or usual care for management. STEP clinic patients receive instructions to self-monitor, a BP monitor, sleep apnea screening, dietary counseling, review of BP monitoring records, and adjustment of medications. Patients are followed by a neurologist and a stroke-trained nurse practitioner. Usual care participants are seen by a neurologist and recommendations for secondary prevention are sent to primary care providers. The primary outcome is the difference in mean daytime ambulatory systolic BP at 6 months, assessed using linear regression analysis. Secondary outcomes include 24 hour ambulatory BP, medication adherence, and medication self efficacy, and composite cardiovascular events.

Ethics and Dissemination:

This study was approved by the Institutional Review Boards at the McGovern Medical School at the University of Texas Health Sciences Center and the Georgetown University School of Medicine. Uninsured and Spanish-speaking patients are included in the study. The trial is registered at ClinicalTrials.gov (NCT02591394).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is designed as a randomized controlled trial of an organizational intervention aimed at improving blood pressure control after stroke. This is a high priority area for stroke prevention.
- This study will include a diverse patient population as we anticipate that more than 30% of eligible patients will be African American who have higher risk for uncontrolled BP and stroke recurrence.
- We will use Bayesian analysis which will allow us to estimate the probability that the intervention is effective at reducing BP.
- We are including uninsured and underserved patients and may therefore have higher attrition rates.
- The trial was designed for patients with mild to moderate post-stroke disability, and results may not be generalizable to patients with more severe strokes.

INTRODUCTION

Improvements in stroke prevention, acute treatment, and organized systems of care for acute stroke are all thought to contribute to declines in stroke mortality observed over the past decade.[1] Nevertheless, there are over 7 million stroke survivors in the United States. With increasing survival after stroke and expected increases in stroke incidence related to population aging, the prevalence of stroke is projected to increase by 3.4 million in 2030.[2, 3] Despite these projections, there has been little emphasis or research on organizing systems of care for stroke survivors.

Post-stroke care should address the unique needs of stroke survivors and prioritize risk factor management for prevention of recurrent stroke. Stroke risk increases after incident stroke, and 25% of incident strokes are recurrent events.[2] Recurrent stroke carries additional risk of morbidity and mortality compared to the incident stroke.[4] Quantitative modeling suggests that up to 80% of vascular events after stroke can be prevented by addressing modifiable risk factors through pharmacologic and behavioral interventions.[5]

Hypertension is the most important risk factor for ischemic stroke and hemorrhagic stroke and reduction in blood pressure (BP) after stroke is associated with markedly reduced risk of stroke recurrence.[6-8] However, available data suggests that hypertension remains poorly controlled after the incident stroke. A report from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study revealed that risk factor awareness and control were poor in participants who self-reported a history of stroke.[9] Stroke survivors were more likely to have undiagnosed hypertension and poorly controlled BP compared to those without prior stroke. Only 66.7% of stroke survivors had controlled BP, and African American stroke survivors were more likely to have undiagnosed hypertension and uncontrolled hypertension (among those treated) than White stroke survivors.

The REGARDs data are supported by other studies that confirm prior ischemic or hemorrhagic stroke. Baseline visit data from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial showed that 56% of ischemic stroke survivors in the US who participated in the study did not have controlled BP two and a half months after stroke.[10] African Americans were more likely to have poorly controlled BP than White Americans in the subset of US participants in SPS3.[10] Investigators from The DiffErenCes in the Imaging of Primary Hemorrhage based on Ethnicity or Race (DECIPHER) project, an observational cohort study based in Washington DC, demonstrated poor BP control 30 days and 1 year after hemorrhagic stroke.[11] In this study, BP was at goal (less than 140/90) for 47.2% of participants at 30 days and for 41.7% one year after stroke. Current practice guidelines give clear recommendations for BP treatment after stroke; however these studies suggest that the recommendations are not effectively implemented in clinical practice.[12]

Interventions for BP Control

Multiple behavioral, psychosocial, environmental and physiologic factors contribute to risk factor control in stroke survivors. In addition to race and socioeconomic status, medication adherence, self-efficacy, marital status, and level of independence are associated with BP control.[9, 10, 13-15] Physiologic factors such as duration of hypertension, differential response to medications according to race and ethnicity, and medical comorbidities such as sleep apnea and chronic kidney disease may also be associated with more resistant hypertension.[16-19] The complexity of these factors and their potential interactions may help explain why BP interventions have been largely ineffective in stroke survivors.

A Cochrane review of randomized clinical trials for post-stroke risk factor management revealed that isolated behavioral and interventions did not impact BP control.[20] Pooled analyses of organizational interventions, such as those incorporating revisions of professional roles, collaboration of multidisciplinary teams, integrated care services, and/or knowledge and quality management protocols demonstrated trends toward improvements in BP control. The effect sizes in the trials assessing change in BP were small (less than 4mmHg change in SBP) and the trials had moderately small sample sizes. Effect sizes might be larger if multiple aspects of care delivery and patient education are addressed in a single intervention. Our aim is to assess the effectiveness of an organizational intervention on BP control in a new type of clinic designed for stroke patients.

STEP Clinic

The Stroke Transitions, Education, and Prevention (STEP) Clinic was developed with the goal of providing integrated care for secondary stroke prevention and stroke complication assessment and management. The patients are managed by a stroke prevention neurologist and a stroke nurse practitioner with training in family medicine. The care team provides stroke education to patients and caregivers, manages uncontrolled risk factors according to protocols and evidence-based guidelines, and supports transitions back into the community.

Patients are referred from a Joint Commission-certified Comprehensive Stroke Center (CSC) at Memorial Hermann Hospital adjacent to the McGovern Medical School in the University of Texas Health Sciences Center. The program serves a diverse population that is approximately 50% non-Hispanic White, 30% African American, and 15% Hispanic American. At the STEPs Georgetown clinic, patients are referred the adjacent MedStar Georgetown University Hospital (MGUH), which is also a CSC, and serves a population that is 55% African American, 42% White, and 3% Asian. The STEP program is not the standard of care for stroke patients, but patients are assigned to the STEP program based on provider availability. Stroke patients who are not referred to the STEP program are scheduled with another neurologist in the outpatient neurology clinic or with a community neurologist. The STEP program has potential to impact risk factor reduction for secondary stroke prevention.

Study Objectives

The primary objective is to compare the effectiveness of post-stroke management in the STEP clinic versus usual care on BP reduction among patients with uncontrolled BP. We hypothesize that the STEP clinic will be more effective than usual care at decreasing mean daytime ambulatory systolic BP by 6 months after randomization.

Secondary objectives will assess the impact of STEP care on additional BP and stroke outcomes. These outcomes include the proportion of patients achieving BP control, the proportion of participants monitoring BP, BP medication adherence, BP self-efficacy, and body mass index. We will also assess the occurrence of cardiovascular events (composite stroke recurrence, myocardial infarction, and vascular death) and use Bayesian analysis to assess the probability of a difference in this outcome between STEP clinic and usual care. We plan to assess modifying effects of race/ethnicity on the relationship between the study intervention and BP outcomes including mean ambulatory BP and the proportion achieving BP control at 6 months. Finally, we will compare the health system costs of follow-up care in the STEP clinic to the costs of usual care. Our goal is to estimate the incremental costs of care with STEP per additional patient with controlled BP according to the American Heart Association (AHA) guidelines.

METHODS AND ANALYSIS

The STEP for Blood Pressure Reduction Study is randomized comparative effectiveness trial with a parallel arm design. Patients are recruited from the Memorial Hermann Hospital System in Houston, Texas and from the MedStar Georgetown University Hospital (site initiated 09/2017). University of Texas Health Science Center (UTHealth) IRB approval was obtained in October 2015 and enrollment began in 11/2015. Georgetown University School of Medicine IRB approval was obtained and enrollment began in November 2017. The trial is registered at ClinicalTrials.gov (NCT02591394). The trial will be completed in December 2018. We used the SPIRIT reporting guidelines for this protocol manuscript.[21]

Eligibility Criteria

Inclusion Criteria are as follows: age ≥ 18, hospitalization for clinical ischemic stroke, hypertensive hemorrhage, or transient ischemic attack, hypertension as evidence by 1) history of hypertension, 2) hospital BP ≥ 140/90 on two or more occasions during hospitalization, or 3) discharge home on BP medication; willingness and ability to follow-up in the stroke clinic, discharge home or to short stay in-patient rehabilitation (<2 weeks) after stroke, and uncontrolled clinic BP two weeks after hospital discharge. A transient ischemic attack diagnosis requires agreement two neurologists. Patients are excluded if they meet any of the following criteria: modified Rankin scale (mRS) > 3 at time of enrollment, terminal illness, chronic kidney disease stage 4 or greater (eGFR < 30 or ESRD), pregnancy, symptomatic flow limiting carotid stenosis without plan for intervention prior to initial clinic visit, rare stroke etiology presumed unrelated to atherosclerotic risk factors (vasculitis, malignancy associated, substance abuse). Patients who were enrolled in other interventional studies were no eligible for the trial.

Consent and Randomization

Study procedures are depicted in Figure 1. Sequential eligible patients are approached for study participation prior to hospital discharge or are called on the telephone shortly after discharge. Informed consent is obtained by research coordinators or study co-investigators prior to discharge for patients approached in the hospital and in the outpatient clinic for patients contacted via telephone. If a patient is unable to give consent due to cognitive impairment, consent is obtained from a legally authorized representative. The final eligibility criterion (uncontrolled BP) is assessed at the initial clinic visit which occurs between 1 week and 30 days of hospital discharge. Uncontrolled BP was initially defined as sitting automated office BP of ≥135/85 mmHg which is equivalent to ≥140/90 by standard office BP assessment.[22, 23] Following release of the 2017 Hypertension Guidelines, uncontrolled BP was redefined as BP ≥130/80 by standard office BP, so this eligibility criterion was changed to BP ≥125/75 by automated office BP.[24] This change was implemented in January 2018 (protocol version 3 – updated on clinicaltrials.gov).

Upon presentation for the initial clinic screening visit, outpatient stroke clinic medical assistants (MAs) perform the initial vital signs assessment. Attended BP measures are obtained by MAs with a calibrated automated BP machine Welch Allen Spots Vital Signs (4200-88E). The MAs also obtain weight and height, then bring the patients to the dedicated research suite for further evaluation with the research coordinator. After the patient and/or caregiver complete the demographic questionnaire, the caregiver(s) are asked to leave the room for the automated BP assessment using BpTRU, one of the most extensively studied automated blood pressure machines.[25-27] The research coordinator applies an appropriately sized cuff to the patient's left upper arm. The patient is positioned so that his or her feet are flat on the floor, back is supported, and legs are uncrossed. The left arm is placed on a table at chest level in the supine

position. The research staff observes the first BP recording to assess adequacy and leaves the patient alone in the room for the remaining five measurements. The machine is programmed to take 6 measurements two minutes apart and to discard the first. The research staff returns after ten minutes to record the BpTRU readings on clinic screening forms. The average of the last five readings is used to determine final eligibility. Patients who are found to have markedly elevated sitting BP at the baseline visit (≥ 170/105) have an immediate visit with MD or stroke NP before randomization.

Following completion of baseline forms (Table 1) eligible patients are randomized to STEP clinic or usual care using the REDCap randomization module. A statistician who is not involved in patient allocation (Pedroza) developed the random sequence with 1:1 allocation ratio and block sizes of 4-8 and loaded the sequence into REDCap. The allocation sequence is not accessible to any other study investigators. Stratification variables include study site, systolic BP at the time of randomization (SBP< 155 vs ≥155) and insurance status. The principal investigators and research coordinators are not blinded to group assignment. The co-investigator reading the ABPMs for the final outcome assessment is blinded to group assignment. The statistician is blinded to group assignment.

Following randomization, participants are scheduled to follow-up in the STEP clinic or usual care within 2 weeks of randomization. Patients randomized to the STEP clinic receive a BP monitor, recommendations for self-monitoring, a folder contained information about stroke risk factors, a BP monitoring brochure, a BP log, a Mediterranean diet brochure and pyramid, and instructions for follow-up. Patients randomized to usual care receive the educational folder and are encouraged to monitor BP.

Study Arms

The STEP arm includes patients randomized to attend the STEP clinic for post-stroke risk factor management. At the initial STEP clinic visit, hospital records are reviewed, and an individualized stroke care plan is developed with the patient (and caretakers if present) based on best-practice guidelines. The BP log is reviewed, and adjustments to medications are made based on BP goals. All patients are screened for medication non-adherence and counseled on the importance of adherence and BP monitoring. The most affordable medications are used as indicated. The BP regimen is reviewed to decrease polypharmacy and multiple daily dosing of medications. All patients are screened for sleep apnea given its association with uncontrolled BP and stroke risk. Patients are counseled and given information on the Mediterranean diet and the importance of decreased sodium intake and exercise for stroke prevention. If BP is not at goal, medications are adjusted, and a 2-4-week BP check or telephone follow-up is scheduled according to BP range (4 weeks for home SBP 125 - 154; 2 weeks for SBP 155 - 174; telephone follow-up and 2-week clinic follow-up for SBP ≥ 175). If BP is at goal at the initial visit, patients will be scheduled for follow-up in 3 months, but BP records are reviewed monthly. More urgent follow-up may also be scheduled according to other factors including depression, clearance for return to work after neuropsychological testing, or sleep study follow-up. The care plan is shared with primary providers and patients are referred to a primary provider if they do not yet have one.

Participants randomized to usual care are scheduled to attend an initial stroke fellow or stroke attending clinic. Risk factor and complication assessment, education, and management are done according to provider practices. Recommendations are sent to referring/primary providers and follow-up is according to provider practices.

Outcome Measures & Assessment Points

The primary outcome is the difference in mean daytime ambulatory SBP at 6 months between groups. Secondary outcomes include the difference in mean daytime ambulatory DBP at 6 months; mean ambulatory night-time SBP and DBP at 6 months; proportion of patients achieving BP control at 6 months using ambulatory and sitting BPs; BP medication adherence at 6 months using Morisky Medication Adherence Scale; [28] depressive symptoms as assessed by PHQ-9 at 6 months;[29] percent of patients monitoring BP at 6 months; satisfaction with social roles and activities, as measured by NeuroQOL short form at 6 months;[30] differences in patient satisfaction with stroke clinic at 6 months using Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys; [31] differences in self-efficacy at 6 months;[32, 33] differences in composite cardiovascular events from enrollment to and study lock; differences in harmful events during the intervention period; direct medical costs and cost-effectiveness.

Baseline demographic and clinical characteristics are abstracted from inpatient charts, supplemented by a demographic case report form collected during the initial visit. Demographic variables include age, sex, self-reported race, self-reported ethnicity, level of education, household income, insurance status, and marital status. Clinical variables include stroke subtype, stroke etiology, prior stroke or TIA, treatment with IV tPA, treatment with intra-arterial intervention, admission National Institutes of Health Stroke Score (NIHSS), pre-stroke (mRS), presence of stroke risk factors (hypertension, diabetes mellitus, tobacco use, hyperlipidemia, obstructive sleep apnea, atrial fibrillation, coronary artery disease, systolic heart failure, substance abuse) other medical co-morbidities, BMI, and number of prescribed medications on admission and at discharge.

Total hospital and clinic costs will be assessed from a health care system perspective. Hospital costs will be estimated by multiplying charges obtained from the 15 Memorial Hermann Health System hospitals and from Georgetown University Hospital by their department-specific cost-to-charge ratios specified in their annual Medicare cost report. Clinic costs will be estimated by applying the RVU-based method to UTH and Georgetown University billing data. Every 3 months until study end, patients will be called to identify any outside hospital and clinic services. In addition, the primary care medical records for those followed outside our center will also be sought. The costs for care received outside will be estimated based on the cost for these services at our center. Medication costs will be estimated based on the prescriptions for each patient and the average wholesale prices in the Red Book Drug References. The STEP program costs will also include the estimated cost for personnel time spent providing the program (above that for usual care) based on time-motion studies and activity and phone call logs. Time costs will be estimated based on staff salary and fringe data. Additional costs associated with the intervention, e.g., costs of print materials, will also be estimated and added to the medical and personnel costs to obtain the total cost of the intervention.

Provider recommendations will be ascertained from the clinic electronic records. In addition to scheduled clinic visits, participants will attend follow-up research assessments 6 months after randomization. At the 6-month visit, the MAs perform the vitals assessment including weight, height, and attended BP. A research coordinator measures sitting BP using BpTRU machine. Patients complete outcome assessments (Table 1). Participants are also sent home with an ambulatory blood pressure monitor and a prepaid FedEx box for return of the monitor. The monitor is mailed back to the research coordinator, and data is downloaded and analyzed by an investigator blinded to patient group. Mean

daytime ambulatory systolic BP (SBP) is assessed as the mean in SBP measurements taken from 8AM until 8PM.

We will assess major clinical outcomes including recurrent stroke, myocardial infarction, and vascular death every 3 months via telephone call (or follow-up visit) from enrollment until data lock. Hospital and Emergency Department (ED) records will be requested if reported at 3-month patient encounters. Additional safety outcomes including syncope, falls, or dizziness/hypotension requiring ED visit/ hospitalization will also be assessed every 3 months until 6 months. At the 6-month follow-up visits, patient clinic records are requested from primary providers to aid in cost analysis.

Participant Retention

Participants are provided with parking passes for research and clinic visits and are provided with compensation for their time for research visits. Home visits for final outcome assessments are offered if participants cannot travel to the clinic. If participants cannot be located for follow-up, we attempt to reach listed emergency contacts before mailing a letter (prior permission) to their homes. We also send holiday cards and newsletters to participants to promote retention.

Statistical Analysis & Sample Size Calculations

Intention to treat analysis will be performed using STATA software.[34] For the primary analysis, linear regression will be used to compare the difference in mean daytime ambulatory SBP between groups using ambulatory SBP as the dependent variable and treatment group, baseline SBP (sitting/ continuous), and insurance status as independent variables. As a secondary analysis of the primary outcome, we will assess treatment effect modification by race/ethnicity using the same linear regression model and introducing an interaction term. Secondary analyses will be used to evaluate additional clinical, behavioral, and safety outcomes.

Linear regression models will be used for continuous variables and logistic regression models will be used for dichotomous variables. For behavioral outcomes (medication adherence/self-efficacy), Wilcoxon rank sum or ordinal regression will be used if proportional hazards assumptions are met. Costs will be compared using multilevel generalized estimating equations (GEE) models with gamma distribution and log link. For safety outcomes, we will use a Poisson regression model; and for composite vascular events, we will also use Bayesian analysis to estimate probability of an event. All models will be adjusted for stratifying variables.

The cost-effectiveness of the program will be estimated by dividing the incremental costs of the STEP program relative to usual care by the incremental number of patients with controlled BP at 6 months. We will also perform sensitivity analyses and probabilistic sensitivity of plausible ranges for costs and effectiveness.

In order to detect a 5mmHg difference in the change in mean ambulatory SBP from baseline to 6 months (power 0.8, α 0.05) using an 11.5 mmHg standard deviation for SBP change, we would need to retain 84 patients in each group. A meta-analysis of BP reduction trials revealed OR for recurrent stroke of 0.78 (0.68, 0.9) with mean change SBP of 5.1 mmHg[7]. Assuming attrition of 15%, we will enroll 100 patients per group.

Patient and Public Involvement

The STEP clinic is designed as a patient-centered care model, which is informed by informal assessments of patient and caregiver preferences and goals during clinic visits. Patients were not formally involved involved in the trial design or conduct. While the primary outcome is a measure of BP, secondary outcomes include measures that relate to quality of life and patient satisfaction. Furthermore, the CAPHS surveys are used to assess patient satisfaction with care provided in the STEP clinic relative to usual care. This survey will assist in our assessment of the burden of the intervention to patients. Upon study completion and analysis of outcomes, a newsletter will be sent to participants to inform them of study results.

ETHICS AND DISSEMINATION

Ethical approval was obtained by the Institutional Review Boards at the McGovern Medical School in Houston (10/2015) and by the Georgetown University School of Medicine 11/2017). The study design, risks and benefits, and patient confidentiality were judged rigorously. The use of protected health information is minimized and any electronic files containing PHI are stored in password protected documents on secure servers. Paper case report forms (CRFs) and consents are stored in locked cabinets in a locked office. The files containing PHI will be retained for 5 years after trial completion. The final dataset will be available to the study principal investigator, the study statistician, and co-investigators by request. A manuscript with the results of the study will be published in a peer-reviewed journal. Trial results will be communicated to participants via a newsletter.

Patients are eligible regardless of insurance status or financial ability to follow-up in the clinic and we guarantee all patients, regardless of randomization assignment, one free clinic visit with a neurologist. If patients report stroke signs or symptoms, have dangerously elevated BP, or report other critical symptoms (chest pain, shortness of breath) during the course of the study, they are treated or referred as appropriate, regardless of clinic assignment.

Data Monitoring and Management

Baseline forms and outcome assessments are obtained using paper CRFs and are subsequently entered a secure REDCap database. The database structure includes range checks for data values, and each data field contains a specific description of the data element including where to find the data in the medical record. Accurate entry of data from paper CRFs into REDCap is verified by co-investigators. Principal investigators review data fields abstracted by research assistants and coordinators.

DISCUSSION

Despite the increasing prevalence of stroke in the coming years, there is little emphasis or research on organizing systems of care for stroke survivors. Multiple behavioral, psychosocial, environmental, and physiological factors contribute to risk factor control.[13, 35-38] Hypertension is a major risk factor for recurrent stroke, and BP reduction is associated with decreased risk of stroke recurrence.[1] However many stroke survivors remain with poorly controlled BP after their initial stroke.[9, 10] The complexity of these risk factors and their potential interactions are not well understood and could explain why isolated BP interventions have been largely ineffective in stroke patients. Post-stroke care should address the unique needs of stroke survivors and prioritize risk factor management for prevention of recurrent stroke. The main goal of the STEP clinic is to implement an organizational intervention on BP control which integrates the various known stroke risk factors into a new type of clinic designed for stroke patients.

If the STEP clinic care is found to be more effective in reducing BP, it may provide a means to improve post-stroke care. A cost analysis comparing cost of the STEP clinic to that of usual care would determine the feasibility of introducing this unique approach to integrated post-stroke care as a standard. The STEP clinic could provide improvements in post-stroke care, risk factor management, and stroke recurrence prevention. This research is needed to determine whether the STEP clinic is more effective in managing stroke risk factors and improving stroke outcomes in comparison to usual care.

Table 1. Data and Outcome Assessment Schedule

	Pre-Screening	Screening	Randomization	Stroke Clinic	3-month	6-month	Safety/ Cardiovascular Outcomes
Visit Number	V0	V1	V1	V2	V3	V4	V5 - V12
Timeline	-30 to -7 days	0	0	2 wk.		6 mo.	Every 3 mo. until data lock
Visit window				+/- 2 wks.	+/- 2 wks.	+/ - 2 wks.	+/- 2 wks.
Location	Hospital	Clinic	Clinic	Clinic	Clinic /Phone	Clinic	Phone
Procedures & Forms							
Pre-screen (Hospital) eligibility / consent	X						
Screen (Clinic) Demographic 2 wk. clinic BP BMI		X X X					
Randomization visit (prior to randomization)							
Demographic form			X				
NIHSS			X			X	
Modified Rankin			X			X	
MOCA			X			X	
Morisky Medication adherence Scale			X			X	
Medication Adherence Self-efficacy Scale			X			X	
Patient Health Questionnaire 9			X			X	
BP monitoring form			X			X	
Patient Satisfaction with social roles and activities (NeuroQol)						X	
Patient Satisfaction (NeuroQol2)						X	
Inpatient data			X				
Clinical data			X	X		X	X
Safety data					X	X	X
ABPM						X	
Claims data (cost)						X	

Blood Pressure (BP); National Institutes of Health Stroke Scale (NIHSS); Montreal Cognitive Assessment (MOCA); Ambulatory Blood Pressure Monitoring (ABPM); week (wk.); month (mo.)

AUTHOR CONTRIBUTIONS:

Anjail Sharrief is the principal investigator for the study. She is responsible for the study design and for overseeing data acquisition. She participated in drafting the manuscript.

Evelyn Hinojosa is a research assistant who participates in data acquisition and abstraction. She participated in manuscript drafting.

Gabretta Cooksey is a research coordinator who participates in patient recruitment, enrollment, follow-up and data acquisition, and who revised the manuscript for important intellectual content.

Munachi Okpala is a nurse practitioner who participates in patient recruitment, enrollment, and follow-up. She participated in study design and manuscript drafting.

Elenir B. Avritscher participates in study design regarding cost effectiveness. She revised the manuscript for important intellectual content.

Claudia Pedroza is a statistician who participated in the design of the study and drafting of the manuscript.

M. Carter Denny is the Principal Investigator at the Georgetown University Medical Center. She participated in study design and participates in data acquisition. She revised the manuscript for important intellectutal content.

Joshua Samuels participated in study design and participates in data analysis and acquisition. He revised the manuscript for important intelectual content.

Jon E. Tyson participated in study design. He contributed important intellectual content to the manuscript.

Sean Savitz participated in study design and contributed important intellectual content to the manuscript.

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COMPETING INTERESTS

None of the authors have declared conflicts of interests.

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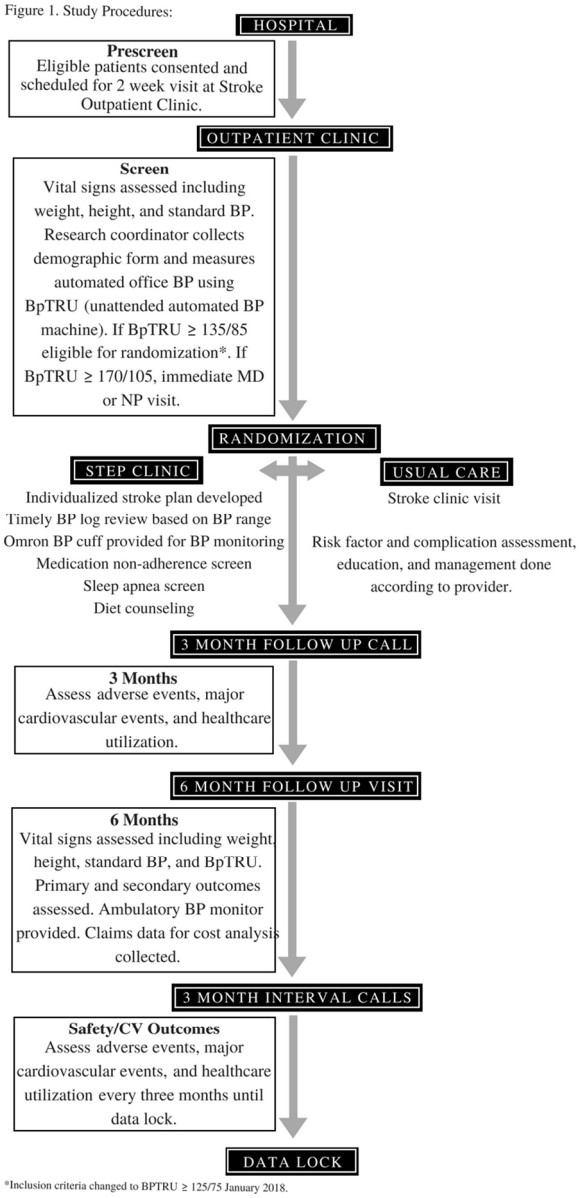
Figure 1. Study Procedures:



*Inclusion criteria changed to BPTRU ≥ 125/75 January 2018.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5, 10
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	304
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, 8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
5Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7, 10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	8

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of	#28	Financial and other competing interests for principal	12

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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DOES CARE IN A SPECIALIZED STROKE PREVENTION CLINIC IMPROVE POST-STROKE BLOOD PRESSURE CONTROL: A PROTOCOL FOR A RANDOMIZED COMPARATIVE EFFECTIVENESS STUDY

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DOES CARE IN A SPECIALIZED STROKE PREVENTION CLINIC IMPROVE POST-STROKE BLOOD PRESSURE CONTROL: A PROTOCOL FOR A RANDOMIZED COMPARATIVE EFFECTIVENESS STUDY

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ABSTRACT

Introduction:
Hypertension is a major risk factor for recurrent stroke, and blood pressure (BP) reduction is associated with decreased risk of stroke recurrence. However, many stroke survivors have poorly controlled BP after their initial stroke. The Stroke Transitions Education and Prevention (STEP) Clinic was established to provide a comprehensive approach to stroke risk factor reduction.

Methods and Analysis:
This randomized comparative effectiveness study was designed to assess the impact of care in the STEP clinic versus usual care on post-stroke BP reduction. Eligible hospitalized patients with ischemic stroke, hemorrhagic stroke, or transient ischemic attack are scheduled for a clinic screening visit within 4 weeks of discharge if they meet baseline inclusion criteria. At the clinic visit, patients who have uncontrolled BP, defined as automated office BP $\geq$ 135/85 mmHg are randomized (1:1) to either the STEP clinic or usual care for management. STEP clinic patients receive instructions to self-monitor, a BP monitor, sleep apnea screening, dietary counseling, review of BP monitoring records, and adjustment of medications. Patients are followed by a neurologist and a stroke-trained nurse practitioner. Usual care participants are seen by a neurologist and recommendations for secondary prevention are sent to primary care providers. The primary outcome is the difference in mean daytime ambulatory systolic BP at 6 months, assessed using linear regression analysis. Secondary outcomes include 24 hour ambulatory BP, medication adherence, and medication self efficacy, and composite cardiovascular events.

Ethics and Dissemination:
This study was approved by the Institutional Review Boards at the McGovern Medical School at the University of Texas Health Sciences Center and the Georgetown University School of Medicine. Uninsured and Spanish-speaking patients are included in the study. The trial is registered at ClinicalTrials.gov (NCT02591394).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is designed as a randomized controlled trial of an organizational intervention aimed at improving blood pressure control after stroke. This is a high priority area for stroke prevention.
- This study will include a diverse patient population as we anticipate that more than 30% of eligible patients will be African American who have higher risk for uncontrolled BP and stroke recurrence.
- We will use Bayesian analysis which will allow us to estimate the probability that the intervention is effective at reducing BP.
- We are including uninsured and underserved patients and may therefore have higher attrition rates.
- The trial was designed for patients with mild to moderate post-stroke disability, and results may not be generalizable to patients with more severe strokes.

INTRODUCTION

Improvements in stroke prevention, acute treatment, and organized systems of care for acute stroke are all thought to contribute to declines in stroke mortality observed over the past decade.[1] Nevertheless, there are over 7 million stroke survivors in the United States. With increasing survival after stroke and expected increases in stroke incidence related to population aging, the prevalence of stroke is projected to increase by 3.4 million in 2030.[2, 3] Despite these projections, there has been little emphasis or research on organizing systems of care for stroke survivors.

Post-stroke care should address the unique needs of stroke survivors and prioritize risk factor management for prevention of recurrent stroke. Stroke risk increases after incident stroke, and 25% of incident strokes are recurrent events.[2] Recurrent stroke carries additional risk of morbidity and mortality compared to the incident stroke.[4] Quantitative modeling suggests that up to 80% of vascular events after stroke can be prevented by addressing modifiable risk factors through pharmacologic and behavioral interventions.[5]

Hypertension is the most important risk factor for ischemic stroke and hemorrhagic stroke and reduction in blood pressure (BP) after stroke is associated with markedly reduced risk of stroke recurrence.[6-8] However, available data suggests that hypertension remains poorly controlled after the incident stroke. A report from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study revealed that risk factor awareness and control were poor in participants who self-reported a history of stroke.[9] Stroke survivors were more likely to have undiagnosed hypertension and poorly controlled BP compared to those without prior stroke. Only 66.7% of stroke survivors had controlled BP, and African American stroke survivors were more likely to have undiagnosed hypertension and uncontrolled hypertension (among those treated) than White stroke survivors.

The REGARDs data are supported by other studies that confirm prior ischemic or hemorrhagic stroke. Baseline visit data from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial showed that 56% of ischemic stroke survivors in the US who participated in the study did not have controlled BP two and a half months after stroke.[10] African Americans were more likely to have poorly controlled BP than White Americans in the subset of US participants in SPS3.[10] Investigators from The DiffErenCes in the Imaging of Primary Hemorrhage based on Ethnicity or Race (DECIPHER) project, an observational cohort study based in Washington DC, demonstrated poor BP control 30 days and 1 year after hemorrhagic stroke.[11] In this study, BP was at goal (less than 140/90) for 47.2% of participants at 30 days and for 41.7% one year after stroke. Current practice guidelines give clear recommendations for BP treatment after stroke; however these studies suggest that the recommendations are not effectively implemented in clinical practice.[12]

Interventions for BP Control

Multiple behavioral, psychosocial, environmental and physiologic factors contribute to risk factor control in stroke survivors. In addition to race and socioeconomic status, medication adherence, self-efficacy, marital status, and level of independence are associated with BP control.[9, 10, 13-15] Physiologic factors such as duration of hypertension, differential response to medications according to race and ethnicity, and medical comorbidities such as sleep apnea and chronic kidney disease may also be associated with more resistant hypertension.[16-19] The complexity of these factors and their potential interactions may help explain why BP interventions have been largely ineffective in stroke survivors.

A Cochrane review of randomized clinical trials for post-stroke risk factor management revealed that isolated behavioral and interventions did not impact BP control.[20] Pooled analyses of organizational interventions, such as those incorporating revisions of professional roles, collaboration of multidisciplinary teams, integrated care services, and/or knowledge and quality management protocols demonstrated trends toward improvements in BP control. The effect sizes in the trials assessing change in BP were small (less than 4mmHg change in SBP) and the trials had moderately small sample sizes. Effect sizes might be larger if multiple aspects of care delivery and patient education are addressed in a single intervention. Our aim is to assess the effectiveness of an organizational intervention on BP control in a new type of clinic designed for stroke patients.

STEP Clinic

The Stroke Transitions, Education, and Prevention (STEP) Clinic was developed with the goal of providing integrated care for secondary stroke prevention and stroke complication assessment and management. The patients are managed by a stroke prevention neurologist and a stroke nurse practitioner with training in family medicine. The care team provides stroke education to patients and caregivers, manages uncontrolled risk factors according to protocols and evidence-based guidelines, and supports transitions back into the community.

Patients are referred from a Joint Commission-certified Comprehensive Stroke Center (CSC) at Memorial Hermann Hospital adjacent to the McGovern Medical School in the University of Texas Health Sciences Center. The program serves a diverse population that is approximately 50% non-Hispanic White, 30% African American, and 15% Hispanic American. At the STEPs Georgetown clinic, patients are referred the adjacent MedStar Georgetown University Hospital (MGUH) in Washington D.C., which is also a CSC, and serves a population that is 55% African American, 42% White, and 3% Asian. The STEP program is not the standard of care for stroke patients, but patients are assigned to the STEP program based on provider availability. Stroke patients who are not referred to the STEP program are scheduled with another neurologist in the outpatient neurology clinic or with a community neurologist. The STEP program has potential to impact risk factor reduction for secondary stroke prevention.

Study Objectives

The primary objective is to compare the effectiveness of post-stroke management in the STEP clinic versus usual care on BP reduction among patients with uncontrolled BP. We hypothesize that the STEP clinic will be more effective than usual care at decreasing mean daytime ambulatory systolic BP by 6 months after randomization.

Secondary objectives will assess the impact of STEP care on additional BP and stroke outcomes. These outcomes include the proportion of patients achieving BP control, the proportion of participants monitoring BP, BP medication adherence, BP self-efficacy, and body mass index. We will also assess the occurrence of cardiovascular events (composite stroke recurrence, myocardial infarction, and vascular death) and use Bayesian analysis to assess the probability of a difference in this outcome between STEP clinic and usual care. We plan to assess modifying effects of race/ethnicity on the relationship between the study intervention and BP outcomes including mean ambulatory BP and the proportion achieving BP control at 6 months. Finally, we will compare the health system costs of follow-up care in the STEP clinic to the costs of usual care. Our goal is to estimate the incremental costs

of care with STEP per additional patient with controlled BP according to the American Heart Association (AHA) guidelines.

METHODS AND ANALYSIS

The STEP for Blood Pressure Reduction Study is randomized comparative effectiveness trial with a parallel arm design. Patients are recruited from the Memorial Hermann Hospital System in Houston, Texas and from the MedStar Georgetown University Hospital (site initiated 09/2017). University of Texas Health Science Center (UTHealth) IRB approval was obtained in October 2015 and enrollment began in 11/2015. Georgetown University School of Medicine IRB approval was obtained and enrollment began in November 2017. The trial is registered at ClinicalTrials.gov (NCT02591394). The trial will be completed in December 2018. We used the SPIRIT reporting guidelines for this protocol manuscript.[21]

Eligibility Criteria

Inclusion Criteria are as follows: age ≥ 18, hospitalization for clinical ischemic stroke, hypertensive hemorrhage, or transient ischemic attack, hypertension as evidence by 1) history of hypertension, 2) hospital BP ≥ 140/90 on two or more occasions during hospitalization, or 3) discharge home on BP medication; willingness and ability to follow-up in the stroke clinic, discharge home or to short stay in-patient rehabilitation (<2 weeks) after stroke, and uncontrolled clinic BP two weeks after hospital discharge. A transient ischemic attack diagnosis requires agreement two neurologists. Patients are excluded if they meet any of the following criteria: modified Rankin scale (mRS) > 3 at time of enrollment, terminal illness, chronic kidney disease stage 4 or greater (eGFR < 30 or ESRD), pregnancy, symptomatic flow limiting carotid stenosis without plan for intervention prior to initial clinic visit, rare stroke etiology presumed unrelated to atherosclerotic risk factors (vasculitis, malignancy associated, substance abuse). Patients who were enrolled in other interventional studies were no eligible for the trial.

Consent and Randomization

Study procedures are depicted in Figure 1. Sequential eligible patients are approached for study participation prior to hospital discharge or are called on the telephone shortly after discharge. Informed consent is obtained by research coordinators or study co-investigators prior to discharge for patients approached in the hospital and in the outpatient clinic for patients contacted via telephone. If a patient is unable to give consent due to cognitive impairment, consent is obtained from a legally authorized representative. The final eligibility criterion (uncontrolled BP) is assessed at the initial clinic visit which occurs between 1 week and 30 days of hospital discharge. Uncontrolled BP was initially defined as sitting automated office BP of ≥135/85 mmHg which is equivalent to ≥140/90 by standard office BP assessment.[22, 23] Following release of the 2017 Hypertension Guidelines, uncontrolled BP was redefined as BP ≥130/80 by standard office BP, so this eligibility criterion was changed to BP ≥125/75 by automated office BP.[24] This change was implemented in January 2018 (protocol version 3 – updated on clinicaltrials.gov).

Upon presentation for the initial clinic screening visit, outpatient stroke clinic medical assistants (MAs) perform the initial vital signs assessment. Attended BP measures are obtained by MAs with a calibrated automated BP machine Welch Allen Spots Vital Signs (4200-88E). The MAs also obtain weight and height, then bring the patients to the dedicated research suite for further evaluation with the research coordinator. After the patient and/or caregiver complete the demographic questionnaire, the caregiver(s) are asked to leave the room for the automated BP assessment using BpTRU, one of the most extensively studied automated blood pressure machines.[25-27] The research coordinator applies an appropriately sized

cuff to the patient's left upper arm. The patient is positioned so that his or her feet are flat on the floor, back is supported, and legs are uncrossed. The left arm is placed on a table at chest level in the supine position. The research staff observes the first BP recording to assess adequacy and leaves the patient alone in the room for the remaining five measurements. The machine is programmed to take 6 measurements two minutes apart and to discard the first. The research staff returns after ten minutes to record the BpTRU readings on clinic screening forms. The average of the last five readings is used to determine final eligibility. Patients who are found to have markedly elevated sitting BP at the baseline visit (≥ 170/105) have an immediate visit with MD or stroke NP before randomization.

Following completion of baseline forms (Table 1) eligible patients are randomized to STEP clinic or usual care using the REDCap randomization module. A statistician who is not involved in patient allocation (Pedroza) developed the random sequence with 1:1 allocation ratio and block sizes of 4-8 and loaded the sequence into REDCap. The allocation sequence is not accessible to any other study investigators. Stratification variables include study site, systolic BP at the time of randomization (SBP< 155 vs ≥155) and insurance status. The principal investigators and research coordinators are not blinded to group assignment. The co-investigator reading the ABPMs for the final outcome assessment is blinded to group assignment. The statistician is blinded to group assignment.

Following randomization, participants are scheduled to follow-up in the STEP clinic or usual care within 2 weeks of randomization. Patients randomized to the STEP clinic receive a BP monitor, recommendations for self-monitoring, a folder contained information about stroke risk factors, a BP monitoring brochure, a BP log, a Mediterranean diet brochure and pyramid, and instructions for follow-up. Patients randomized to usual care receive the educational folder and are encouraged to monitor BP.

Study Arms

The STEP arm includes patients randomized to attend the STEP clinic for post-stroke risk factor management. At the initial STEP clinic visit, hospital records are reviewed, and an individualized stroke care plan is developed with the patient (and caretakers if present) based on best-practice guidelines. The BP log is reviewed, and adjustments to medications are made based on BP goals. All patients are screened for medication non-adherence and counseled on the importance of adherence and BP monitoring. The most affordable medications are used as indicated. The BP regimen is reviewed to decrease polypharmacy and multiple daily dosing of medications. All patients are screened for sleep apnea given its association with uncontrolled BP and stroke risk. Patients are counseled and given information on the Mediterranean diet and the importance of decreased sodium intake and exercise for stroke prevention. If BP is not at goal, medications are adjusted, and a 2-4-week BP check or telephone follow-up is scheduled according to BP range (4 weeks for home SBP 125 - 154; 2 weeks for SBP 155 - 174; telephone follow-up and 2-week clinic follow-up for SBP ≥ 175). If BP is at goal at the initial visit, patients will be scheduled for follow-up in 3 months, but BP records are reviewed monthly. More urgent follow-up may also be scheduled according to other factors including depression, clearance for return to work after neuropsychological testing, or sleep study follow-up. The care plan is shared with primary providers and patients are referred to a primary provider if they do not yet have one.

Participants randomized to usual care are scheduled to attend an initial stroke fellow or stroke attending clinic. Risk factor and complication assessment, education, and management are done according to provider practices. Recommendations are sent to referring/primary providers and follow-up is according to provider practices.

Outcome Measures & Assessment Points

The primary outcome is the difference in mean daytime ambulatory SBP at 6 months between groups. Secondary outcomes include the difference in mean daytime ambulatory DBP at 6 months; mean ambulatory night-time SBP and DBP at 6 months; proportion of patients achieving BP control at 6 months using ambulatory and sitting BPs; BP medication adherence at 6 months using Morisky Medication Adherence Scale; [28] depressive symptoms as assessed by PHQ-9 at 6 months;[29] percent of patients monitoring BP at 6 months; satisfaction with social roles and activities, as measured by NeuroQOL short form at 6 months;[30] differences in patient satisfaction with stroke clinic at 6 months using Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys; [31] differences in self-efficacy at 6 months;[32, 33] differences in composite cardiovascular events from enrollment to and study lock; differences in harmful events during the intervention period; direct medical costs and cost-effectiveness.

Baseline demographic and clinical characteristics are abstracted from inpatient charts, supplemented by a demographic case report form collected during the initial visit. Demographic variables include age, sex, self-reported race, self-reported ethnicity, level of education, household income, insurance status, and marital status. Clinical variables include stroke subtype, stroke etiology, prior stroke or TIA, treatment with IV tPA, treatment with intra-arterial intervention, admission National Institutes of Health Stroke Score (NIHSS), pre-stroke (mRS), presence of stroke risk factors (hypertension, diabetes mellitus, tobacco use, hyperlipidemia, obstructive sleep apnea, atrial fibrillation, coronary artery disease, systolic heart failure, substance abuse) other medical co-morbidities, BMI, and number of prescribed medications on admission and at discharge.

Total hospital and clinic costs will be assessed from a health care system perspective. Hospital costs will be estimated by multiplying charges obtained from the 15 Memorial Hermann Health System hospitals and from Georgetown University Hospital by their department-specific cost-to-charge ratios specified in their annual Medicare cost report. Clinic costs will be estimated by applying the RVU-based method to UTH and Georgetown University billing data. Every 3 months until study end, patients will be called to identify any outside hospital and clinic services. In addition, the primary care medical records for those followed outside our center will also be sought. The costs for care received outside will be estimated based on the cost for these services at our center. Medication costs will be estimated based on the prescriptions for each patient and the average wholesale prices in the Red Book Drug References. The STEP program costs will also include the estimated cost for personnel time spent providing the program (above that for usual care) based on time-motion studies and activity and phone call logs. Time costs will be estimated based on staff salary and fringe data. Additional costs associated with the intervention, e.g., costs of print materials, will also be estimated and added to the medical and personnel costs to obtain the total cost of the intervention.

Provider recommendations will be ascertained from the clinic electronic records. In addition to scheduled clinic visits, participants will attend follow-up research assessments 6 months after randomization. At the 6-month visit, the MAs perform the vitals assessment including weight, height, and attended BP. A research coordinator measures sitting BP using BpTRU machine. Patients complete outcome assessments (Table 1). Participants are also sent home with an ambulatory blood pressure monitor and a prepaid FedEx box for return of the monitor. The monitor is mailed back to the research

coordinator, and data is downloaded and analyzed by an investigator blinded to patient group. Mean daytime ambulatory systolic BP (SBP) is assessed as the mean in SBP measurements taken from 8AM until 8PM.

We will assess major clinical outcomes including recurrent stroke, myocardial infarction, and vascular death every 3 months via telephone call (or follow-up visit) from enrollment until data lock. Hospital and Emergency Department (ED) records will be requested if reported at 3-month patient encounters. Additional safety outcomes including syncope, falls, or dizziness/hypotension requiring ED visit/ hospitalization will also be assessed every 3 months until 6 months. At the 6-month follow-up visits, patient clinic records are requested from primary providers to aid in cost analysis.

Participant Retention

Participants are provided with parking passes for research and clinic visits and are provided with compensation for their time for research visits. Home visits for final outcome assessments are offered if participants cannot travel to the clinic. If participants cannot be located for follow-up, we attempt to reach listed emergency contacts before mailing a letter (prior permission) to their homes. We also send holiday cards and newsletters to participants to promote retention.

Statistical Analysis & Sample Size Calculations

Intention to treat analysis will be performed using STATA software.[34] For the primary analysis, linear regression will be used to compare the difference in mean daytime ambulatory SBP between groups using ambulatory SBP as the dependent variable and treatment group, baseline SBP (sitting/ continuous), and insurance status as independent variables. As a secondary analysis of the primary outcome, we will assess treatment effect modification by race/ethnicity using the same linear regression model and introducing an interaction term. Secondary analyses will be used to evaluate additional clinical, behavioral, and safety outcomes.

Linear regression models will be used for continuous variables and logistic regression models will be used for dichotomous variables. For behavioral outcomes (medication adherence/self-efficacy), Wilcoxon rank sum or ordinal regression will be used if proportional hazards assumptions are met. Costs will be compared using multilevel generalized estimating equations (GEE) models with gamma distribution and log link. For safety outcomes, we will use a Poisson regression model; and for composite vascular events, we will also use Bayesian analysis to estimate probability of an event. All models will be adjusted for stratifying variables.

The cost-effectiveness of the program will be estimated by dividing the incremental costs of the STEP program relative to usual care by the incremental number of patients with controlled BP at 6 months. We will also perform sensitivity analyses and probabilistic sensitivity of plausible ranges for costs and effectiveness.

In order to detect a 5 mmHg difference in the change in mean ambulatory SBP from baseline to 6 months (power 0.8, α 0.05) using an 11.5 mmHg standard deviation for SBP change, we would need to retain 84 patients in each group. The 5 mmHg difference was chosen because a meta-analysis of BP reduction trials revealed OR for recurrent stroke of 0.78 (0.68, 0.9) with mean change SBP of 5.1 mmHg[7]. Assuming attrition of 15%, we will enroll 100 patients per group.

Patient and Public Involvement

The STEP clinic is designed as a patient-centered care model, which is informed by informal assessments of patient and caregiver preferences and goals during clinic visits. Patients were not formally involved involved in the trial design or conduct. While the primary outcome is a measure of BP, secondary outcomes include measures that relate to quality of life and patient satisfaction. Furthermore, the CAPHS surveys are used to assess patient satisfaction with care provided in the STEP clinic relative to usual care. This survey will assist in our assessment of the burden of the intervention to patients. Upon study completion and analysis of outcomes, a newsletter will be sent to participants to inform them of study results.

ETHICS AND DISSEMINATION

Ethical approval was obtained by the Institutional Review Boards at the McGovern Medical School in Houston (10/2015) and by the Georgetown University School of Medicine 11/2017). The study design, risks and benefits, and patient confidentiality were judged rigorously. The use of protected health information is minimized and any electronic files containing PHI are stored in password protected documents on secure servers. Paper case report forms (CRFs) and consents are stored in locked cabinets in a locked office. The files containing PHI will be retained for 5 years after trial completion. The final dataset will be available to the study principal investigator, the study statistician, and co-investigators by request. A manuscript with the results of the study will be published in a peer-reviewed journal. Trial results will be communicated to participants via a newsletter.

Patients are eligible regardless of insurance status or financial ability to follow-up in the clinic and we guarantee all patients, regardless of randomization assignment, one free clinic visit with a neurologist. If patients report stroke signs or symptoms, have dangerously elevated BP, or report other critical symptoms (chest pain, shortness of breath) during the course of the study, they are treated or referred as appropriate, regardless of clinic assignment.

Data Monitoring and Management

Baseline forms and outcome assessments are obtained using paper CRFs and are subsequently entered a secure REDCap database. The database structure includes range checks for data values, and each data field contains a specific description of the data element including where to find the data in the medical record. Accurate entry of data from paper CRFs into REDCap is verified by co-investigators. Principal investigators review data fields abstracted by research assistants and coordinators.

DISCUSSION

Despite the increasing prevalence of stroke in the coming years, there is little emphasis or research on organizing systems of care for stroke survivors. Multiple behavioral, psychosocial, environmental, and physiological factors contribute to risk factor control.[13, 35-38] Hypertension is a major risk factor for recurrent stroke, and BP reduction is associated with decreased risk of stroke recurrence.[1] However many stroke survivors remain with poorly controlled BP after their initial stroke.[9, 10] The complexity of these risk factors and their potential interactions are not well understood and could explain why isolated BP interventions have been largely ineffective in stroke patients. Post-stroke care should address the unique needs of stroke survivors and prioritize risk factor management for prevention of recurrent stroke. The main goal of the STEP clinic is to implement an organizational intervention on BP control

which integrates the various known stroke risk factors into a new type of clinic designed for stroke patients.

If the STEP clinic care is found to be more effective in reducing BP, it may provide a means to improve post-stroke care. A cost analysis comparing cost of the STEP clinic to that of usual care would determine the feasibility of introducing this unique approach to integrated post-stroke care as a standard. The STEP clinic could provide improvements in post-stroke care, risk factor management, and stroke recurrence prevention. This research is needed to determine whether the STEP clinic is more effective in managing stroke risk factors and improving stroke outcomes in comparison to usual care.

Figure 1 Legend:
This figure illustrates the timeline and procedures for study screening, enrollment, and follow-up.

Table 1. Data and Outcome Assessment Schedule

	Pre-Screening	Screening	Randomization	Stroke Clinic	3-month	6-month	Safety/ Cardiovascular Outcomes
Visit Number	V0	V1	V1	V2	V3	V4	V5 - V12
Timeline	-30 to -7 days	0	0	2 wk.		6 mo.	Every 3 mo. until data lock
Visit window				+/- 2 wks.	+/- 2 wks.	+/ - 2 wks.	+/- 2 wks.
Location	Hospital	Clinic	Clinic	Clinic	Clinic /Phone	Clinic	Phone
Procedures & Forms							
Pre-screen (Hospital) eligibility / consent	X						
Screen (Clinic) Demographic 2 wk. clinic BP BMI		X X X					
Randomization visit (prior to randomization)							
Demographic form			X				
NIHSS			X			X	
Modified Rankin			X			X	
MoCA			X			X	
Morisky Medication adherence Scale			X			X	
Medication Adherence Self-efficacy Scale			X			X	
Patient Health Questionnaire 9			X			X	
BP monitoring form			X			X	
Patient Satisfaction with social roles and activities (NeuroQol)						X	
Patient Satisfaction (NeuroQol2)						X	
Inpatient data			X				
Clinical data			X	X		X	X
Safety data					X	X	X
ABPM						X	
Claims data (cost)						X	

Blood Pressure (BP); National Institutes of Health Stroke Scale (NIHSS); Montreal Cognitive Assessment (MoCA); Ambulatory Blood Pressure Monitoring (ABPM); week (wk.); month (mo.)

AUTHOR CONTRIBUTIONS:

Anjail Sharrief is the principal investigator for the study. She is responsible for the study design and for overseeing data acquisition. She participated in drafting the manuscript.

Evelyn Hinojosa is a research assistant who participates in data acquisition and abstraction. She participated in manuscript drafting.

Gabretta Cooksey is a research coordinator who participates in patient recruitment, enrollment, follow-up and data acquisition, and who revised the manuscript for important intellectutal content.

Munachi Okpala is a nurse practitioner who participates in patient recruitment, enrollment, and follow-up. She participated in study design and manuscript drafting.

Elenir B. Avritscher participates in study design regarding cost effectiveness. She revised the manuscript for important intellectual content.

Claudia Pedroza is a statistician who participated in the design of the study and drafting of the manuscript.

M. Carter Denny is the Principal Investigator at the Georgetown University Medical Center. She participated in study design and participates in data acquisition. She revised the manuscript for important intellectutal content.

Joshua Samuels participated in study design and participates in data analysis and acquisition. He revised the manuscript for important intelectual content.

Jon E. Tyson participated in study design. He contributed important intellectual content to the manuscript.

Sean Savitz participated in study design and contributed important intellectual content to the manuscript.

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COMPETING INTERESTS

None of the authors have declared conflicts of interests.

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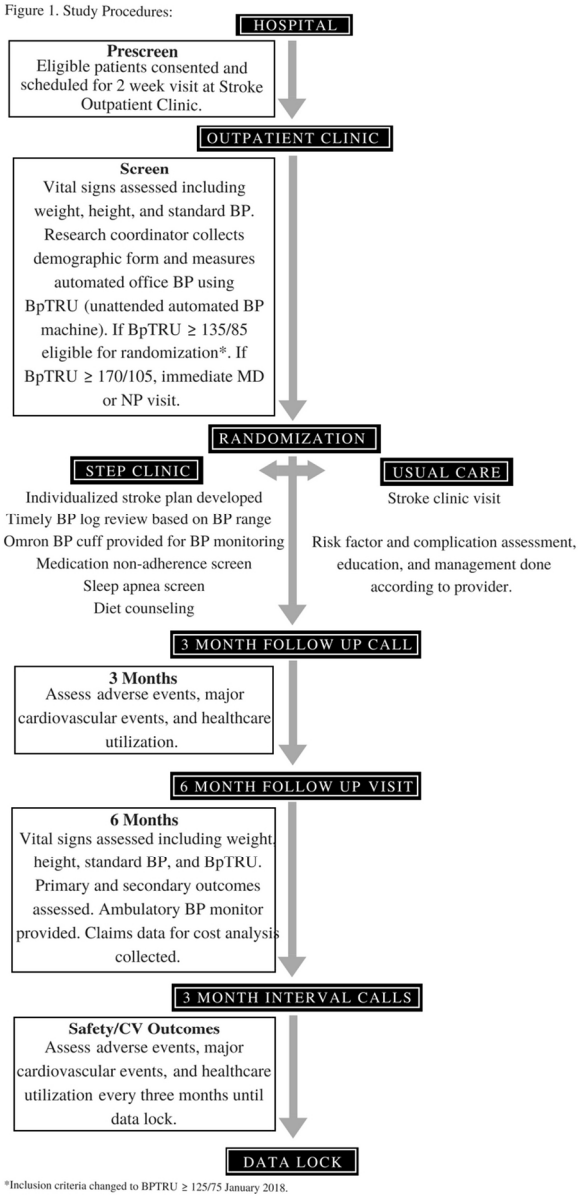
Figure 1. Study Procedures:



*Inclusion criteria changed to BPTRU ≥ 125/75 January 2018.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5, 10
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	304
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, 8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
5Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7, 10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	8

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of	#28	Financial and other competing interests for principal	12

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a