1.0 General Information

1.1 *Please enter the full title of your study:

An evaluation of clinical pharmacist-led intervention on clinical outcomes in patients with ischemic stroke

1.2 *Please enter the Short Study Title:

CPCRS stroke study

2.0 Add Department(s)

2.1 List of Departments associated with this study:

Primary Dept?	Department Name
	KPCO - Pharmacy

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Olson, Kari, PharmD

3.2 If applicable, please select the Protocol Staff personnel:

A) Additional Investigators

Delate, Thomas, PhD, MS
Co-Investigator
Dowd, Mary
Co-Investigator
Hutka, Kara
Co-Investigator
Lamprecht Jr., Don, PharmD
Co-Investigator
Merenich, John
Co-Investigator
Rasmussen, Jon
Co-Investigator
Ruppe, Leslie

Co-Investigator
Sandhoff, Brian
Co-Investigator
Schimmer, Jennifer, PharmD
Co-Investigator

B) Research Support Staff

No Research Staff have been added.

3.3 *Please add a Project Manager:

1. Kurz, Deanna, BA, CCRP

The Project Manager(s) will receive all important system notifications along with the Principal Investigator. (e.g. The study contact(s) are typically either the Research Assistant or the Principal Investigator themselves).

4.0 Level One Research Personnel

4.1 All Level One Research Staff involved in this study must be listed by name in Section 3.0 of this application. Please return to Section 3.0 if you need to identify any additional Level One Research Staff as defined here.

Level One Research Staff: Likelihood of harm, protocol violation, or unanticipated problems is high if these individuals fail to follow the protocol and/or comply with regulations and KP policy for the protection of human subjects. Please see the HRPPP website (click on help tab for link) for more information and a list of characteristics that distinguish individuals who are in the Level One category.

5.0 Submission Type

5.1 What type of project are you submitting?

- (•) Human Subject Research
- ( ) Exemption Request
- ( ) Interregional/ Interinstitutional Research Application
- ( ) Single Patient Use
- ( ) Emergency Use
- ( ) Humanitarian Use Device

○ Human Subjects research assessment form

6.0 IRB Submission

6.1 Is this the Principal Investigator's first submission to the KPCO IRB?

○ Yes ◉ No

6.2 Is this study going towards an academic degree or school requirement?

○ Yes ◉ No

6.3 Please enter the start and end dates for the entire length of the study.

Study start date:
08/02/2010
Study end date:
12/31/2016

6.4 Please indicate the level of risk associated with this study.

◉ *Minimal risk
○ Greater than minimal risk
○ Unknown

7.0 Outside PI

7.1 Will there be an outside Principal Investigator involved with this study?

○ Yes ◉ No

8.0 Participating Institutions

8.1 Will any outside institutions be participating in this research study?

○ Yes ◉ No
If yes, please enter the names of the participating institutions.

9.0 Vulnerable Populations
Please indicate the role, if any, that the following groups might have in this study.

9.1 Pregnant women, fetuses, in vitro fertilization:

○ Targeted
◉ Excluded
○ Included
Comments:

9.2 Children (<18 years old):

- ○ Targeted
- ◉ Excluded
- ○ Included

Comments:

9.3 Decisionally/Cognitively impaired:

- ○ Targeted
- ◉ Excluded
- ○ Included

Comments:

9.4 Economically or educationally disadvantaged:

- ○ Targeted
- ○ Excluded
- ◉ Included

Comments:

9.5 Non-English speakers:

- ○ Targeted
- ○ Excluded
- ◉ Included

Comments:

9.6 Employees of Kaiser Permanente:

- ○ Targeted
- ○ Excluded
- ◉ Included

Comments:

9.7 Elderly:

- ○ Targeted
- ○ Excluded
- ◉ Included

Comments:

9.8 Prisoners:

- ○ Targeted
- ◉ Excluded
- ○ Included

Comments:

9.9 If there is another vulnerable population the study plans on working with, that is not listed above, please enter it below.

Leave blank if not applicable.

- ○ Targeted
- ○ Excluded
- ○ Included

Comments:

10.0 Research Use of Internet

10.1 Will the internet be used to either transmit data OR provide access to data within or outside of KPCO OR communicate with participants, including e-mail?

- ◉ Yes ○ No

11.0 Research Use of Internet

11.1 Will participants be asked to provide any information using the internet?

- ◉ Yes
- ○ No
- ○ N/A (data only, no participants)

12.0 Research Use of Internet

12.1 What measures will be taken to ensure the web server hosting the internet site is protected? (e.g. physical security, firewalls, software patches/updates, penetration drills, etc.)

KP.org - My Health Manager will be the internet site utilized to communicate with study participants. See below for their security information.

High (128-bit) security encryption
This Web site has security measures in place to help protect against the loss, misuse, or alteration of information under our control. These measures include encryption of data using the Secure Socket Layer (SSL) system, and using a secured messaging service when we send you personal information electronically. Use and disclosure of health information includes using the information to provide treatment to the individual, to make payments for such treatment, and to conduct ongoing quality improvement activities. Our use and disclosure of an individual's personal information (including health information) is limited as required by state and federal law.

12.2 Will a password or other secure authorization method be used to allow access to the web site?

(•) Yes ( ) No

13.0 Research Use of Internet

13.1 How will user passwords be distributed?

Per KPCO policy. We will not be making any changes to communication via KP.org based on study activities.

13.2 How will passwords and web access be terminated?

Per KPCO policy for activity on KP.org. For study purposes as well as standard of care, participants can request not to be contacted via e-mail. Contact can be made via phone or letter per patients request.

14.0 Research Use of Internet

14.1 Will the user session(s) be encrypted?

(•) Yes ( ) No

15.0 Research Use of Internet

15.1 What method of encryption will be used? (SSL, PKI, etc.)

SSL

15.2 Will a minimum level of 128-bit encryption be used?

(•) Yes ( ) No

16.0 Research Use of Internet

16.1 Who will have administrative access to data on the web server? (provide names, study roles, and organizational affiliations)

Name	Study Role	Organizational Affiliations
Kari L Olson, BSc(Pharm), Pharm D	PI	KPCO
Jon Rasmussen, Pharm D	Co-I	KPCO
Kara Hutka, Pharm D	Co-I	KPCO

Don Lamprecht, Pharm D	Co-I	KPCO
Leslie Ruppe, Pharm D	Co-I	KPCO
Jennifer Schimmer, Pharm D	Co-I	KPCO
Brian Sandhoff, Pharm D	Co-I	KPCO
MaryBeth Dowd, Pharm D	Co-I	KPCO
Tom Delate, PhD	Co-I	KPCO
John A. Merenich, MD	Co-I	KPCO
Deanna Kurz, BA	PM	KPCO

16.2 What administrative safeguards exist to restrict unauthorized and unnecessary access?

See terms and conditions posted at KP.org for all administrative safeguards to secure access.

https://members.kaiserpermanente.org/kpweb/disclaimer/entrypage.do

16.3 Who is the application owner (who maintains the application)?

Internet Services Group,department of Kaiser Foundation Health Plan,

17.0 Research Use of Internet

17.1 Will e-mail be used to contact participants?

(•) Yes ( ) No

18.0 Research Use of Internet

18.1 How can participants be assured the communication is from an authorized person?

KP.org secure e-mail will be used if participant chooses this mode of communication per current HC identification as active or not.

19.0 Research Use of Internet

19.1 Will participants be asked to contact investigators using e-mail?

(•) Yes ( ) No

20.0 Research Use of Internet

20.1 How will participants be authenticated to adequately ensure the source of the e-mail communication?

KP.org security and access is sufficient to ensure authenticity of e-mail communication.

21.0 Research Use of Internet

21.1 Does the study consent form discuss potential risks to privacy associated with use of e-mail?

( ) Yes
(•) No
( ) Not Applicable

Additional Comments:

The potential risks of using KP.org are identified in the "Terms and conditions" when registering for site use. There is no change to that risk with the study activities.

22.0 Research Use of Internet

22.1 Will e-mail be used to send study data to investigators, vendors or others inside or outside KP?

(•) Yes ( ) No

23.0 Research Use of Internet

23.1 Will the e-mail be encrypted?

(•) Yes ( ) No

23.2 Will attachments to the e-mail be encrypted or password protected?

(•) Yes ( ) No

24.0 Research Use of Internet

24.1 If automated email routing systems are used, what security controls will be in place? Describe your testing and disaster recovery procedures.

N/A

25.0 Research Use of Internet

25.1 Will contractors or vendors have access to study participant's personal identifiable or confidential information?

○ Yes ◉ No

26.0 Research Use of Internet

26.1 What is the volume and frequency of data being transmitted via the internet (including e-mail)?

Only Kaiser Permanente study personnel will have access to the data and will only be transmitted behind the KPCO firewall. Data transfers will be as needed to complete all study activity, analysis and manuscript preparation.

27.0 Research Use of Internet

27.1 Who is responsible for ensuring that KP policies and procedures for confidentiality and security are followed for this project? Provide name of the person responsible and his/her professional position and affiliation.

Name	Title	Affiliation
Kari L Olson, BSc(Pharm), Pharm D	PI	KPCO

27.2 Who is responsible for security administration for the information technology associated with this project? Provide the name of the person responsible and his/her professional position and affiliation.

Name	Title	Affiliation
Kaiser Foundation Health Plan	Web manager	KP

28.0 Data Management

28.1 Will data storage be internal (within KP firewall)?

◉ Yes ○ No

If yes, describe file storage on LAN (eg, data warehouse, storage facility).

29.0 Data Management

29.1 Please describe how access to study data will be restricted to study personnel.

Only Kaiser Permanente study personnel will have access to the data and the data will be password protected and/or kept in a locked cabinet.

29.2 Who will have access to study data?

Name	Title	Affiliation
Kari L Olson, BSc(Pharm), Pharm D	PI	KPCO
Jon Rasmussen, Pharm D	CO-I	KPCO
Kara Hutka, Pharm D	CO-I	KPCO
Don Lamprecht, Pharm D	CO-I	KPCO
Leslie Ruppe, Pharm D	CO-I	KPCO
Jennifer Schimmer, Pharm D	CO-I	KPCO
Brian Sandhoff, Pharm D	CO-I	KPCO
MaryBeth Dowd, Pharm D	CO-I	KPCO
Tom Delate, PhD	CO-I	KPCO
John A. Merenich, MD	CO-I	KPCO

29.3 What administrative safeguards will be in place? (describe process for incident management and/or reporting of security breach)

ALL DATA WILL BE KEPT LOCKED AND OR PASSWORD PROTECTED AND WILL BE DEIDENTIFIED AT THE EARLIEST OPPORTUNITY. INCIDENT MANAGEMENT AND REPORTING WILL FOLLOW THE COMPLIANCE REGULATIONS SET FORTH IN THE "PRIVACY AND SECURITY INCIDENT MANAGEMENT" GUIDELINES.

29.4 Who will manage the study data?

Kari L Olson, BSc(Pharm), Pharm D

30.0 Background and Significance

30.1 Provide information about the background and significance of this study.
For help with this question please click on the help button.

Stroke is the third leading cause of death in the United States (U.S.) and the most common life-threatening neurologic disorder.[1] Stroke is a leading cause of long-term disability and results in significant individual and societal financial burdens. In 2006, stroke accounted for 1 of every 18 deaths and ischemic stroke accounted for 87% of all strokes.[1] In the U.S., out of the approximately 795,000 people who develop a stroke each year, approximately 185,000 (23%) are recurrent events.[1] After the first year, the average annual risk for recurrent stroke is 4%.[2] Patients who survive at least 30 days after a first-ever stroke, have an average annual risk of death of 9.1%, much of the risk due to nonstroke cardiovascular disease.[3]

Pharmacotherapeutic treatment regimens involving lipid-lowering therapy with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins"),[4-7] antihypertensive agents (particularly, angiotensin converting enzyme (ACE) inhibitors and thiazide-type diuretics),[8-11] antiplatelet therapy,[12-16] and smoking cessation interventions have all been shown to improve long-term clinical outcomes in this high-risk population. Implementing these interventions at the time of hospitalization for stroke has demonstrated improvement in long-term adherence to the interventions.[17,18] National guidelines also recommend these therapies for secondary stroke prevention.[19,20]

Several meta-analyses have examined the effects of statins on stroke. A meta-analysis of 26 randomized trials with statins involving more than 90,000 patients reported a relative odds reduction for stroke of 21% (95% CI, 27% to 15%).[21] The size of the beneficial effect on stroke reduction was associated with the degree of low-density lipoprotein-cholesterol (LDL-C) lowering achieved, with each 10% LDL-C lowering estimated to reduce the risk of stroke by 15.6% (95% CI, 6.7 to 23.6). Similarly, the Cholesterol Treatment Trialists' Collaborators examined 14 randomized statin trials also involving more than 90,000 patients, and reported that statins were associated with a 17% relative risk reduction in the incidence of first stroke (95% CI, 0.78 to 0.88) with a trend towards proportion reductions in stroke being associated with greater reductions in LDL-C.[22] Similar results were reported in a meta-analysis of 27 trials comparing statin to placebo, which found a 17% reduction in all cerebrovascular events (95% CI, 0.76 to 0.91) and a 21% reduction in ischemic stroke (95% CI, 0.63 to 0.99).[23]

More recently, the first prospective study examining the effect of statins for the secondary prevention of ischemic stroke was completed. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators randomly assigned approximately 5000 patients with a recent ischemic or hemorrhagic stroke or transient ischemic attack (TIA) and LDL-C levels >100 mg/dL to atorvastatin 80 mg daily or placebo.[7] The median follow-up was

approximately 5 years and the mean LDL-C for patients assigned to atorvastatin and placebo was 73 mg/dL and 129 mg/dL, respectively. After adjustment for baseline factors, patients randomized to atorvastatin had a 16% relative risk reduction for the primary end point of nonfatal or fatal stroke (HR 0.84; 95% CI, 0.71 to 0.99). On the basis of this trial, the American Heart Association and American Stroke Association (AHA/ASA) advocate for intensive lipid-lowering with statins in patients with atherosclerotic stroke or TIAs to reduce the risk of stroke and cardiovascular events.[19,20]

Hypertension is the most important modifiable risk factor for the primary and secondary prevention of stroke. It is estimated that more than 25% of strokes may be attributed to uncontrolled hypertension.[24] Treatment with evidence based antihypertensive medications are recommended by the AHA/ASA for the prevention of recurrent stroke and other vascular events.[19,20] The AHA/ASA also recommends that antihypertensive medications be considered for patients with stroke with no history of hypertension as clinical trial data suggest a benefit irrespective of the blood pressure value.[19,20]

The Heart Outcomes Prevention Evaluation (HOPE) study compared the effects of ramipril (ACE inhibitor) to placebo in nearly 10,000 patients considered to be at high-risk for vascular events.[25] The mean systolic blood pressure of the patients in both treatment and placebo arms was <140 mmHg and the mean diastolic blood pressure was <80 mmHg (SD ± 20 and 11, respectively). Of the subset of patients with a prior stroke or TIA, those receiving ramipril had a 24% relative risk reduction (95% CI, 5 to 40) for stroke, myocardial infarction (MI), or vascular death.[25] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated the effects of blood pressure lowering with ACE inhibitor alone or in combination with a thiazide diuretic in patients with a recent (i.e., previous 5 years) history of stroke or TIA.[10] The combination of ACE inhibitor and thiazide diuretic reduced the risk of recurrent stroke by 43% (95% CI, 30 to 54).[10]

Despite the evidence supporting the use of various therapeutic interventions within the ischemic stroke population, a significant proportion of patients continue to have uncontrolled risk factors and remain undertreated.[26-30] A recent prospective study of more than 4933 high-risk patients reported that, as compared to patients with coronary artery disease, patients with cerebrovascular disease are undertreated and thus less likely to achieve blood pressure (45.3% vs. 57.3%; $p<0.001$) and lipid (19.4% vs. 30.5%; $p<0.001$) targets.[28] Although the reasons for the so-called "treatment gap" have not been explored specifically within this population, data from studies within the coronary artery disease population suggest that provider, patient and health care system factors likely all contribute.

To help address the treatment gap, the American Heart Association developed **Get With The Guidelines®–Stroke (GWTGS) to** help ensure continuous quality improvement of acute stroke treatment and ischemic stroke prevention.[30,31] The program focuses on care team protocols to ensure that patients are treated and discharged from hospital appropriately. It is available for implementation at acute care hospitals nationwide. While GWTGS has improved care delivery among patients admitted to hospital with acute stroke,[31,32] it does not focus on long-term delivery of care for ambulatory patients. Evaluation of health care delivery systems which focus on long-term care are needed to identify efficient, cost-effective methods that can improve outcomes of patients with ischemic stroke.

Clinical pharmacy specialists are in an ideal position to assist medical teams in the management of patients with ischemic stroke. Given their extensive and specialized knowledge regarding medication efficacy, safety, and cost-effective use as well as their ability to critically review, interpret and apply the results from clinical studies to patient care, clinical pharmacy specialists have the potential to have a significant impact on stroke care delivery. There are numerous opportunities for clinical pharmacy specialists to become more extensively involved in the delivery of care to these high-risk patients. However, to-date there are few studies demonstrating the impact of clinical pharmacy specialists on outcomes of patients with stroke. One study utilized pharmacists for managing modifiable risk factors among patients with ischemic stroke.[33] Patients with ischemic stroke (n=160) were randomized to usual care or a 1-hour pharmacist intervention education program. Differences in blood pressure, glucose, and lipid profiles before and after the study were evaluated. The proportion with adequate blood pressure, lipid, and glucose control in the UC and intervention groups at the end of the study was 43% vs. 83% (p=0.001), 27% vs. 40% (p=0.16), and 46% vs. 35% (p=0.040), respectively. This study was not powered to evaluate differences in the outcomes evaluated, did not apply an intensive intervention over time, and the "dose" of intervention was likely not enough to see improvements in processes of care. ***In contrast to studies in coronary artery disease, there is currently insufficient knowledge on how best to deliver optimal care to secondary prevention to patients with ischemic stroke.***

31.0 Hypothesis and Objectives

31.1 Explain the hypothesis and objectives for this study. - **For help with this section of the form please click on the help button.**

Aim 1: Conduct a randomized, controlled, study of a clinical pharmacist-led disease management intervention for patients with a history of non-cardioembolic ischemic stroke compared to usual care.

Hypothesis 1a: More patients in the clinical pharmacy specialist-led disease management group will achieve their lipid and blood pressure goals compared to the "Usual Care" group.

Hypothesis 1b: Fewer patients randomized to the clinical pharmacy specialist-led disease management group will have recurrent cardiovascular events or death compared to patients in the "usual care" group.

Hypothesis 1c: More patients with ischemic stroke will receive appropriate secondary prevention care using evidence-based medications in the intervention group compared to usual care.

Significance: To our knowledge, this will be the first, prospective, randomized study to evaluate the impact of a clinical pharmacist disease management program on both surrogate and clinical outcomes for patients with non-cardioembolic ischemic stroke.

32.0 Study Methods

32.1 Provide a description of how the study question (hypothesis) will be tested and how participants or their health information will be involved in the study.

For help with this question please click on the help button.

Study Design: This will be a randomized, controlled study comparing a clinical pharmacist-led disease management intervention by the Clinical Pharmacy Cardiac Risk Service (CPCRS) to usual care (UC). Randomization will be 1:1 and will occur at the patient-level.

Patient Selection Criteria

Inclusion Criteria:

All active KPCO non-institutionalized patients from the Denver/Boulder metropolitan area with a validated non-cardioembolic ischemic stroke diagnosis within the past 5 years who:

§ Are ≥18 years of age at the time of informed consent, and

§ Are Eligible for CPCRS enrollment, and

§ Have uncontrolled blood pressure (the most recent value >130/80 mmHg noted in the medical record), and/or

§ Have last LDL-C, within the previous 365 days, that is ≥100 mg/dL (the most recent will be used).

Exclusion Criteria:

Patients will be excluded if:

§ → >85 years of age at the time of consent,

§ Have transient ischemic attacks, subarachnoid hemorrhage, intracerebral hemorrhage, or cardioembolic stroke as their only validated stroke history,

§ Die within 30 days of stroke,

§ Are already followed by the Clinical Pharmacy Cardiac Risk Service (CPCRS). These patients either have a history of coronary artery disease (acute MI, CABG, percutaneous coronary interventions, and/or coronary catheterizations), are at high-risk for CAD as determined by the cardiologist, or have peripheral arterial disease,

§ Have a diagnosis of dementia or a terminal illness in which the life expectancy is <3 years per the discretion of the primary care provider,

§ Have notation in the medical record of memory issues or other conditions which, based on the judgment of study staff, suggest that the patient may not be able to provide informed consent,

§ Are pregnant or breast-feeding, or

§ Do not consent to participate

§ Currently listed on the "Do Not Call List"

Both English and Spanish speaking patients will be eligible for participation.

Patient Screening for Eligibility: All patients with ICD-9 codes 430.XX to 438.XX (estimated to be approximately 15,000 patients at KPCO) will be administratively identified from KPCO claims databases starting January 1, 2000 and administratively pulled into a HealthTrac®-*Stroke* registry. Each patient included in the registry will undergo a validation process to ensure stroke type and event dates are accurate (Appendix I). This validation process will be similar to that used for the HealthTrac®-*CAD* registry already used by CPCRS.

Data collection

The HealthTrac-*Stroke*® registry, electronic medical record and KPCO administrative, claims, pharmacy, and laboratory data will be used for data collection and documentation of study group assignments. Patient characteristics to be collected at baseline (within 6-months of enrollment date) include demographics (age, sex, race (at time of enrollment), co-morbidities (hypertension, cardiac disease history, atrial fibrillation, diabetes mellitus, depression, sleep apnea, smoking status [current, past (quit ≥5 years ago), never]. Cardiovascular-related medications and dosages will be identified from administrative KPCO medication databases. These medications will include lipid-lowering medications, antihypertensive medications, (diuretics, β-blockers, ACE inhibitors/angiotensin receptor blockers, calcium channel blockers, and others), antiplatelet agents (i.e., aspirin, clopidogrel, ticlopidine, dipyridamole/ASA, prasugrel). Laboratory data will be extracted from the KPCO laboratory results administrative database. The number and type of encounters (clinic, procedure, hospital, emergency room, clinical documentation, email, telephone, etc) over the study period will be collected for both groups.

33.0 Data Analysis

33.1 Describe the data analysis plan for this study. For help with this question please click on the help button.

STUDY Outcome Measures

The outcome measures selected for the study are based on AHA/ASA guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack.[19,20] The surrogate measures to be evaluated are the "ABCs" which include Antiplatelet/antithrombotic therapy, Blood pressure control, Cholesterol control, and Smoking cessation. These variables will be evaluated at various time points during the study in part to evaluate the CPCRS processes of care for attaining surrogate measures in the short-term and maintenance of these outcomes long-term compared to Usual Care. Surrogate outcome measures will be evaluated at 1 and 3 years after randomization.

Primary Outcome Measure

The primary outcome will be the proportion of patients in each group who attain recommended LDL-C and BP goals 3 years after randomization. Patients in both groups will be mailed reminder letters within 60 days of their study end date to have their fasting lipid profile drawn or blood pressure measured, as necessary. If patients do not have the necessary values obtained within 30 days of their study end date, they will be mailed a second reminder letter. In the event,

patients still do have the required laboratories and/or blood pressure values, patients will be called by the study staff.

The LDL-C goal will be <100 mg/dL for all patients as recommended by clinical practice guidelines.[19,20] The proportion of patients with an LDL-C <70 mg/dL in each group will also be reported. A fasting lipid profile dated ± 60 days of the study end date will be utilized for study outcome assessment. In the event that a fasting lipid profile is not or can not be obtained, a non-fasting lipid panel, if available, will be utilized for study outcome assessment. However, all attempts will be made to obtain a fasting lipid profile for study purposes.

There are no definitive BP goals outlined in national practice guidelines. The Kaiser Permanente National Hypertension Clinical Practice Guideline committee recommends a blood pressure <130/80 mmHg. For study purposes, a blood pressure goal <130/80 mmHg will be utilized. The most recent clinic visit blood pressure ± 60 days of the study end date will be used for outcome assessment. In the event there are multiple readings on the same day, the lowest reading will be used. Blood pressure values taken at the time of a medical procedure or emergency department visit will not be counted or be included for outcome assessment. Patients for whom a blood pressure is not available in the medical record, will be asked to make an appointment to attend either a blood pressure group visit or attend a walk-in blood pressure visit at their clinic. These visits have no co-pays for patients. The lowest blood pressure reading obtained during these visits will be used for study purposes.

2 **Secondary Outcome Measures**

A number of secondary outcome measures will be evaluated to evaluate the effectiveness and safety of the CPCRS intervention as compared to Usual Care.

2.1 Major cardiovascular events

2.1.a. Cardiovascular events will include fatal or non-fatal stroke, coronary events, or revascularization procedures. Stroke will include either ischemic or hemorrhagic. Coronary events will include acute myocardial infarction ± percutaneous coronary intervention, percutaneous coronary intervention, or coronary artery bypass graft surgery (CABG) surgery. Revascularization procedures include percutaneous coronary intervention, coronary artery bypass graft surgery (CABG) surgery, carotid endarterectomy, interarterial stent insertion. Events will be captured administratively using ICD-9 and/or CPT codes and will be reviewed by individuals blinded the randomization scheme. Cases of fatal or non-fatal strokes will be reviewed and confirmed by a neurologist as will the stroke classification (ischemic, hemorrhagic, or unknown). Coronary event cases will be reviewed by an individual at CPCRS (not associated with the study) who has expertise in validating coronary events. Major cardiovascular events will be evaluated as a combined end point as well as individually.

2.1.b. Hospitalizations: Hospitalizations for any reason will be collected over the study period for all patients.

2.1.c. Death: Death will be captured through KPCO administrative databases. Cause of death will be determined by death certificates and classified as any-cause or cardiovascular. If not cause of death is noted on the death certificate, the cause will be assumed to be cardiovascular. Cardiovascular deaths will include death from cardiac causes, ruptured aortic aneurysm, or peripheral vascular disease. Sudden deaths will be regarded as cardiovascular unless an alternative explanation is documented.

3. Tertiary Outcomes

Tertiary outcome measures will describe the effectiveness and safety of the intervention as compared to Usual care.

.3.1. Lipid and Blood Pressure Control

In addition to evaluating the primary outcome of BP and LDL control at year 3, these parameters will also be evaluated year 1 after randomization. For lipid parameters, in addition to the LDL-C goal attainment, NonHDL goal attainment (<130/ mg/dL) and the LDL/HDL ratio <2.0) will be evaluated at years 1 and year 3. No additional contacts will be made to obtain these readings outside of the intervention/usual care practices. Values available in the medical record ± 180 days of year 1 will be used for assessing this outcome. If no values are available in this timeframe, just the available data will be analyzed and compared.

3.2. Evidence-Based Medications

3.2.a. Antiplatelet/Antithrombotic Medications: Prescriptions for antiplatelet therapy (dipyridamole/aspirin, ticlopidine, clopidogrel and/or prasugrel) or anticoagulation therapy (warfarin) will be assessed at 1 and 3 years after randomization for both groups. Patients will be considered persistent to these medications if days supply/sold date (± 15 days) overlaps the date of the 1 and 3 year timeframes. Aspirin use will only be collected by patient report at baseline and at 3 years for both groups. This is an over-the-counter medication that is not tracked in the KPCO prescription databases. The only way to capture ASA data will be through patient report.

3.2.b Antihyperlipidemic Medications: In addition to lipid goal attainment, the prescription antihyperlipidemic medications and dose the patient is taking will be collected at 1 and 3 years for both groups. The medications will be classified as statin, fibric acid derivatives, ezetimibe, nicotinic acid (i.e. Niaspan®), bile acid sequestrants, or other. Patients will be considered persistent to the lipid-lowering therapy if the days supply overlaps the date (± 15 days) of their FLP result at each time point.

3.2.c. Antihypertensive Medications: In addition to blood pressure goal attainment, the antihypertensive medications and dose the patient is taking will be collected at each time point (1 and 3 years). Medications will be classified into therapeutic classes (i.e. thiazide diuretic, ACE inhibitor, β-blocker, calcium channel blocker, etc). Patients will be considered to be persistent to antihypertensive therapy if the days supply (± 15 days) overlaps the date of their blood pressure assessment.

3.3. Smoking Cessation: Smoking cessation will be assessed for both groups at baseline and study end (year 3) per patient report and will be coded as current, past (quit 5 years ago), or never. Smoking will include any nicotine products (cigarettes, cigars, pipes) and chewing tobacco. The quantity smoked or second-hand smoke exposure will not be captured.

Sample Size Calculation

For the primary outcome of proportion at both BP and LDL-c goals at year 3, and based on prior studies,[28] we estimate that 45% of patients in the Usual Care group will meet the end point at 3-years and conservatively estimate that 60% the CPCRS intervention will meet the end point. An enrollment number of 173 patients per group will be required, with a two-sided alpha of 0.05 and power of 80%. To account for about a 20% dropout rate, the number will be inflated to 200 patients per group.

It is estimated that approximately 5200 patients will have validated stroke, of which

4200 will have ischemic stroke (both cardioembolic and non-cardioembolic and approximately 2500 will have non-cardioembolic ischemic stroke. We anticipate that with this pool of patients, we should be able to meet this sample size calculation.

Statistical Analysis

All statistical analyses will be performed on an intention-to-treat basis utilizing SAS (SAS, Cary, NC) statistical software. Baseline subject characteristics for each study group will be reported as means, medians, and standard deviations for interval- and ratio-level variables (e.g., age, length of time between events, mean lipid levels) and percentages for nominal- and ordinal-level data (e.g., sex, cardiovascular event history). All patients who completed follow-up in their randomized intervention assignment at years 1 and years 3 (as outlined in outcomes assessment) will be included regardless of whether they interacted with CPCRS or not. Interval-level outcome variables will be assessed for normality of their distributions and appropriate tests (e.g., t-test, rank-sum test) will be used to assess differences in mean values between groups. Study outcomes will dichotomized as yes/no (e.g., reached BP & LDL goal levels yes/no, persistent

with lipid-lowering therapy yes/no). To assess differences in proportions between groups on dichotomous outcome variables, Pearson's chi-square test of association will be utilized. An alpha < 0.05 will be considered statistically significant.

34.0 Risks and Benefits

34.1 Provide justification for the risks and benefits of this study. For help with this question please click on the help button.

THE ADDITIONAL DISCOMFORT FROM STUDY PROCEDURES WILL BE REASONABLE IN RELATION TO SOC. WHILE THE BENEFIT TO AN INDIVIDUAL PATIENT IS UNKNOWN AT THIS TIME, THE RISKS ARE NEGLIGIBLE AND THE INFORMATION GAINED WILL PROVIDE IMPORTANT INSIGHT. THEREFORE, WE CONCLUDE THAT RISK: BENEFIT IS REASONABLE FOR THIS STUDY.

35.0 Study Type

35.1 Please identify what type of research study this is:

- ○ Data Only
- ◉ Enrollment
- ○ Both/Other

36.0 Enrollment

36.1 Estimated number of participants:

Within KPCO:
400
Total all sites:
400
Comments:

36.2 Will non-Kaiser Permanente members be enrolled in this study at KPCO?

○ Yes ◉ No
Comments:

36.3 Does this study use an investigational DRUG or DEVICE?

- ☐ Investigational Drug
- ☐ Investigational Device
- ☑ Neither

37.0 Enrollment

37.1 Check the participant documents that will be used in this study:

- [x] Consent Form(s)
- [ ] Authorization Form
- [ ] Surveys/Questionnaires
- [x] Contact/Recruitment Letter
- [ ] Post Cards
- [ ] Recruitment Flyer
- [x] Phone scripts
- [x] Other (Please list below)

37.2 Please list the other participant documents:

Reminder letters

37.3 Please list the study documents that have not been developed yet.

38.0 Enrollment

38.1 Special study procedures: Select all that may apply.

These procedures should be explained clearly in the Informed Consent , if applicable.

- [ ] Tissue collection for research testing (Includes blood and bodily fluids)
- [ ] Tissue/specimen banking for future testing
- [ ] Genetic testing
- [ ] HIV testing
- [ ] Gene therapy
- [ ] Videos, audiotapes, or photographs taken of study participants
- [ ] Other
- [x] Not applicable

Other special study procedures:

39.0 Informed Consent Questionnaire

39.1 What type of approval are you requesting? (Select all that apply)

- [ ] Approval of draft consent/assent forms attached to this application
- [ ] A waiver of informed consent
- [x] An alteration of informed consent
- [ ] A waiver of signed informed consent

40.0 Informed Consent Questionnaire

40.1 Does the proposed research present no more than minimal risk to the study participants?

(•) Yes ( ) No

40.2 Could there be any legal or psychosocial risk to the study participants?

( ) Yes (•) No

40.3 Explain how the waiver or alteration of informed consent will not adversely affect the rights and welfare of participants.

The study team is requesting an alteration of written informed consent for this study. The CPCRS conducts the majority of their clinical care via telephone and do not have routine face-to-face contact with patients. During the telephone consent process, patients will be asked specific questions concerning study activities to verify comprehension and autonomy. The patient will have time to discuss participation with family and friends and a follow up call can be completed to address this request. For those who agree to participate, a letter summarizing the study and related activies and who to contact for questions will be mailed.

Therefore, the study team is asking for approval for telephone consent (Appendix III) and requesting a waiver of HIPAA from the IRB. All study staff have completed the required research training.

40.4 Explain how the research cannot practically be carried out without a waiver or alteration of informed consent.

As stated, the The CPCRS conducts the majority of their clinical care via telephone and do not have routine face-to-face contact with patients. CPCRS is located at Central Support Services which is not set up for in-person patient visits therefore we are asking for the alteration of informed consent.

40.5 Describe any plans you may have to provide pertinent information to the study participants at a later date (including any study findings/results). If the study is not designed to yield information that would be pertinent to the participants, please explain why.

We have no plans to provide study participants with information pertinent to the study at this time, however, if results are published, participants would have access to the results. Also, the results of this study may influence the care patients receive. Results will be shared/discussed with providers in aggregate form.

41.0 Informed Consent Questionnaire

41.1 Check the elements of informed consent that you wish to remove or alter. Provide an explanation in the associated text box. Check all that apply.

- [ ] A statement that the study involves research.
- [ ] An explanation of the purpose of the research.
- [ ] The expected duration of the subject's participation.
- [ ] A description of the procedures to be followed.
- [ ] Identification of the procedures that are experimental.
- [ ] A description of any reasonably foreseeable risks or discomforts to the participant.
- [ ] A description of any benefits to the participant or to others that may reasonably be expected from the research.
- [ ] A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
- [ ] A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- [ ] For research involving more than minimal risk, an explanation as to whether any compensation will be provided. Also an explanation as to whether any medical treatments will be provided if injury occurs, and if so, what kind, at whose expense, and where further information may be obtained.
- [x] An explanation of whom to contact for answers to pertinent questions about the research participant's rights. Also whom to contact in the event of a research-related injury to the subject (standard statement, research questions, rights, injury).

We provide this information in the study summary sheet mailed to all participants.

- [ ] A statement that participation is voluntary, refusal to participate in the study will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled (standard statement).

42.0 HIPAA Privacy Rule

42.1 What type of approval are you requesting? (Check all that apply)

- [ ] Approval of the draft privacy rule authorization attached to this application.
- [ ] No Protected Health Information (PHI) will be used or disclosed.
- [ ] Data will be pulled in the form of a deidentified or limited data set.
- [ ] Waiver of the requirement to obtain HIPAA Privacy Rule authorization to use PHI to develop a deidentified or limited data set.
- [ ] Waiver of the requirement to obtain HIPAA Privacy Rule authorization to use PHI for participant identification and screening.
- [ ] Waiver of the requirement to obtain HIPAA Privacy Rule authorization to use PHI for participant recruitment.
- [x] Waiver of the requirement to obtain HIPAA Privacy Rule authorization for the entire study.

43.0 HIPAA Privacy Rule

43.1 The waiver is being requested for (check one):

- (•) The USE of Protected Health Information (PHI) by members of the KPCO workforce within the KPCO region
- ( ) The USE of PHI by members of the KPCO workforce within the KPCO region and DISCLOSURE of PHI to an individual or entity outside of KPCO

44.0 HIPAA Privacy Rule

44.1 Does the use and/or disclosure of PHI involve more than minimal risk to the privacy of participants?

( ) Yes (•) No

44.2 Describe the plan to protect identifiable information from improper use and disclosure:

PHI data will be stored in a password protected database. The data sets collected will be stripped of patient identifiers and a unique non-identifying study ID will be assigned to each patient. This list of ID numbers will be stored in a separate location from the database containing PHI. Only the study staff will have access to this password protected database. Patient profiles will be assessed only for the minimum set of variables required for study activity and analysis. Patient identifiers will not be used in any presentation or publication containing results. Upon study completion, PHI information will be destroyed to ensure complete confidentiality. PHI will not be disclosed.

44.3 Describe the plan to destroy the identifiable information at the earliest opportunity. If there is a health, research, or legal justification for retaining the identifiers, please describe.

We do not anticipate any Health, research or legal reason to retain patient identifiers following end of study activities and publication. All identifiable information will be destroyed at the earliest opportunity.

44.4 Explain how the research could not feasibly be conducted without the waiver.

Due to the current location and CPCRS patient care process, it is not feasible to conduct in-person visits for this study activity.

44.5 Explain how the research could not feasibly be conducted without access to and use of the PHI:

Identification and screening of patient eligibility, and study recruitment could not be done without the waiver. In addition, the CPCRS location and department process for patient care, individual patient visits could not be completed to meet study enrollment. Therefore this study could not be completed with out the waiver.

44.6 Explain how access to PHI will be the minimum necessary to conduct the research:

Only the minimum PHI neccesary to complete study activities will be obtained.

44.7 Provide a description of the PHI that will be used and a description of the PHI that will be disclosed (if applicable):

Description of PHI that will be used and disclosed (if applicable):

The HealthTrac-*Stroke*® registry, electronic medical record and KPCO administrative, claims, pharmacy, and laboratory data will be used for data collection and documentation of study group assignments. Patient characteristics to be collected at baseline (within 6-months of enrollment date) include demographics (age, sex, race (at time of enrollment), co-morbidities (hypertension, cardiac disease history, atrial fibrillation, diabetes mellitus, depression, sleep apnea, smoking status [current, past (quit ≥5 years ago), never]. Cardiovascular-related medications and dosages will be identified from administrative KPCO medication databases. These medications will include lipid-lowering medications, antihypertensive medications, (diuretics, β-blockers, ACE inhibitors/angiotensin receptor blockers, calcium channel blockers, and others), antiplatelet agents (i.e., aspirin, clopidogrel, ticlopidine, dipyridamole/ASA, prasugrel). Laboratory data will be extracted from the KPCO laboratory results administrative database. The number and type of encounters (clinic, procedure, hospital, emergency room, clinical documentation, email, telephone, etc) over the study period will be collected for both groups.
No PHI will be disclosed.

45.0

Study Procedures

45.1 Study procedures involving human subjects: For help with this section of the form please click on the help button.

Kaiser Permanente Colorado (KPCO) is a group-model, closed-panel, non-profit managed care organization that provides integrated health care services to over 500,000 members in Colorado. KPCO has integrated administrative, claims, and laboratory databases and electronic medical records. Additionally, KPCO uses internal pharmacies with automated pharmacy records which include all medications dispensed at each outpatient facility.

In 1998, KPCO instituted a comprehensive cardiac care program for all patients with coronary artery disease (CAD), called the Clinical Pharmacy Cardiac Risk Service (CPCRS). Like GWTG, CPCRS was designed to provide patients with CAD comprehensive evidence-based lifestyle and medication support at the earliest opportunity. CPCRS is managed by clinical pharmacy specialists focused on the long-term medication management of patients with CAD.[34-36] Since inception, over 21,000 patients have been enrolled in

CPCRS. Currently, CPCRS is initiated in all KPCO patients with CAD and only limited by patient or provider choice (<1% of all eligible patients).

The goal of the CPCRS is to assist primary care physicians and cardiology teams with the implementation and long-term management of all evidence-based treatment strategies, such as lipid-lowering and antiplatelet therapy, ß-blockers post-myocardial infarction, and ACE inhibitors in all eligible KPCO patients with CAD. Therapeutic lifestyle modification and medication adherence are emphasized at every contact with each patient enrolled in the service. The majority of care is delivered via telephone. The number of patient contacts varies depending on the patient's control of blood pressure, lipids, and diabetes but ranges from approximately once to 6 times per year. Patients receive letters informing them of lipid and blood pressure results received and summary of any therapeutic recommendations made. Patients remain in CPCRS indefinitely or until they leave the health plan.

CPCRS utilizes a shared, web-based tracking database which houses data from all validated patients enrolled and is uploaded daily with pertinent administrative, laboratory, pharmacy, diagnosis/procedure, vital sign, and demographic data. The database is utilized for ongoing clinical and population management, patient tracking, and quality improvement activities.

CPCRS has published outcomes of their care in numerous publications.[35-41]. While these studies highlight CPCRS success in achieving LDL-C and blood pressure goals within the CAD population, because analysis have been limited to retrospective, data-only analysis as there is no control group by which to compare CPCRS, issues of bias exist. With CPCRS expanding care delivery to patients with ischemic stroke, there is an opportunity to evaluate prospectively, using a strong study design which addresses any issues of bias or confounding, CPCRS care on patient outcomes.

Intervention (CPCRS) Group: The intervention will utilize clinical pharmacy specialists in CPCRS. The intervention will be similar to what is applied to patients with CAD. CPCRS will ensure patients have regular laboratory monitoring (i.e. lipids) and blood pressure measures, initiated on appropriate lipid-lowering and antihypertensive medications, and receive follow-up in a timely manner. CPCRS staff will order evidence-based lipid-lowering and/or antihypertensive medications, adjust doses, and order follow-up laboratory parameters, as necessary under pre-approved regional treatment protocols (Appendix V). Patients will be monitored for medication adherence and adverse effects. Patients receive dietary, exercise, and smoking cessation counseling verbally and through mailing of pre-printed Kaiser Permanente approved, patient education pamphlets, as necessary per the discretion of the clinical pharmacy specialist. Patients requiring more intensive dietary counseling will be referred to dieticians, education classes, or other appropriate resources offered at KPCO. Primary care providers will be informed of all medication initiations or

dosage adjustments via documentation in the electronic medical record. Any clinical scenarios that the clinical pharmacy specialist is unclear on how to proceed will have requests for consultation of either the PCP, neurologist or the CPCRS medical director. The primary mode of communication between CPCRS and patients will be via telephone or e-mail through kp.org. Patients who achieve their lipid and blood pressure treatment goals will be placed into long-term "CPCRS-maintenance" which will require less intensive CPCRS management. Patients will have laboratories and blood pressure checked annually per regular treatment protocols, until study end.

Usual Care: Patients randomized to Usual Care will continue to receive interventions/procedures they normally receive according to standard/usual care practices.

Follow-up for Laboratories and Blood Pressure Values: The HealthTrac-*Stroke*® disease registry will be used to schedule follow-up contacts in order to minimize the number of subjects lost to follow-up. Letters will be mailed to subjects in the Intervention group reminding him/her to have appropriate laboratories completed, as necessary, using standard CPCRS letters. Patients who fail to have laboratories drawn after 2 mailed reminder letters separated by 1-month will be marked "noncompliant" in the database and receive reminders every 6 months thereafter.

For patients in the Usual Care group, no reminder letters will be sent. However for assessment of lipid and blood pressure control at 3 years (primary outcome) for both groups, reminder letters will be mailed, if necessary (Appendix VI).

Study end: All patients will be followed for 3 years from randomization or until the first occurrence of KPCO termination date, cardiovascular event, or death.

45.2 Explain the Participant Identification and Recruitment Procedures. For assistance with this question please click on the HELP BUTTON.

Patient Screening for Eligibility: All patients with ICD-9 codes 430.XX to 438.XX (estimated to be approximately 15,000 patients at KPCO) will be administratively identified from KPCO claims databases starting January 1, 2000 and administratively pulled into a HealthTrac®-*Stroke* registry. Each patient included in the registry will undergo a validation process to ensure stroke type and event dates are accurate (Appendix I). This validation process will be similar to that used for the HealthTrac®-*CAD* registry already used by CPCRS.

Staff at CPCRS will manually review the electronic medical record for each patient in the registry to ensure the ICD-9 code for stroke is accurate according to detailed procedures (Appendix I). Patients with history that indicates

transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, or cardioembolic stroke will be coded as "TIA" or "Hemorrhage" or "Cardioembolic" stroke, respectively, in the registry and not eligible for study screening or entry. Patients will be considered to have ischemic stroke if there is documentation in the medical record, hospital discharge summary or otherwise, indicating the patient had symptoms consistent with a stroke, for example but not limited to sudden numbness or weakness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination, sudden, severe headache with no known cause) and/or imaging (MRI or CT scan) of clinically relevant brain lesions or there is documentation from a physician noting the patient has had a stroke.[12] It is estimated that approximately 5200 patients will have validated stroke, of which 4200 will have ischemic stroke (both cardioembolic and non-cardioembolic) and approximately 2500 will have non-cardioembolic ischemic stroke.

The HealthTrac-*Stroke*® registry will contain patient demographics, care providers, medical history including stroke history and type, laboratory, medication, and procedure data, and select outcomes (recurrent strokes, TIAs, acute MI, coronary artery bypass graft (CABG) surgery, percutaneous coronary interventions, carotid endarterectomies, and coronary catheterizations). All eligible patients with a validated non-cardioembolic ischemic stroke diagnosis in the HealthTrac®-*Stroke* registry will be screened for study eligibility by study personnel.

45.3 Explain the process for obtaining informed consent and HIPAA Authorization and Participant Compensation. For assistance completing this section please click on the HELP BUTTON.

Patients who meet screening criteria will be contacted initially via mail to inform them of the study (Appendix II). After 14 days, patients will be contacted by trained study staff . The staff member will attempt to contact each potential participant up to 6 times (not including a busy signal) dispersed over no longer than 2 weeks. Calls will be made between the hours of 8 AM and 8 PM, unless the participant requests otherwise. Potential participants will not be contacted more than once per day except to return calls. Voicemail messages will be left on the first attempt and after every third attempt at least 3 days after any prior message, up to three total voicemail messages. If an attempt is made prior to 3 days after a message, the attempt will be documented, but no message will be left.

For patients with access to kp.org, one of the 6 contacts to patients will be through kp.org (Appendix VII)

Patients who do not wish to participate will be asked to call within 14 days of receiving the letter stating so. Patients who do not call will be contacted by telephone to further describe the study, evaluate their eligibility, and obtain verbal informed consent (Appendix III) for study participation and randomization. All questions regarding the study will be answered by one of the study staff members. If patients wish to discuss their involvement in the study with their primary care physician, family member or other individual, they will be given that right and rescheduled for another time. Any concerns by study staff about the patients' mental capacity to understand the consent and study procedures during the consent process will preclude a patients' eligibility for study inclusion.

After a patient agrees to participate, the study personnel will access the randomization table for the next available randomization assignment and notify the patient. All patients who agree to participate will be mailed a summary of the study with study contact information for their files (Appendix IV).

For patients who speak Spanish, a translator (Pacific Interpreters @ 1-800-264-1552) will be utilized following standard KP policies to obtain consent. Staff who will be obtaining consent have experience using this mechanism for communicating with patients.

The study team is requesting an alteration of written informed consent for this study. The CPCRS conducts the majority of their clinical care via telephone and do not have routine face-to-face contact with patients. Therefore, the study team is asking for approval for telephone consent (Appendix III) and requesting a waiver of HIPAA from the IRB. All study staff have completed the required research training.

A waiver of HIPAA Authorization is also being requested to analyze data in aggregate for all non-participants (those who are eligible and those who refuse to participate). A limited data set for these patients will be created so that we may characterize the initial pull of eligible study patients with those who do and do not agree to be contacted for study participation. The following data will be collected administratively: age, sex, co-morbidities, and current antihyperlipidemic and antihypertensive medications.

Once patients have consented to participate in the study, they will be randomized in 1:1 fashion at the patient-level to the Intervention (i.e. CPCRS care) or Usual Care groups using a pre-determined computer-generated list of random numbers. The randomization scheme will be stored in a separate electronic file, stored behind KPCO's firewall. Patients will be notified of the treatment group they have been assigned to. For patients in the CPCRS arm, study personnel will notify the CPCRS supervisor of the patients study enrollment and the supervisors will enroll the patient into CPCRS using standard procedures as for other patients.

Study participation for patients in both groups will be documented in the Problem List of HealthConnect. The note will include that patients are enrolled in a clinical trial, the arm to which they are randomized and contact information in case there are questions related to the study.

7. Study Procedures:

Intervention (CPCRS) Group: The intervention will utilize clinical pharmacy specialists in CPCRS. The intervention will be similar to what is applied to patients with CAD. CPCRS will ensure patients have regular laboratory monitoring (i.e. lipids) and blood pressure measures, initiated on appropriate lipid-lowering and antihypertensive medications, and receive follow-up in a timely manner. CPCRS staff will order evidence-based lipid-lowering and/or antihypertensive medications, adjust doses, and order follow-up laboratory parameters, as necessary under pre-approved regional treatment protocols (Appendix V). Patients will be monitored for medication adherence and adverse effects. Patients receive dietary, exercise, and smoking cessation counseling verbally and through mailing of pre-printed Kaiser Permanente approved, patient education pamphlets, as necessary per the discretion of the clinical pharmacy specialist. Patients requiring more intensive dietary counseling will be referred to dieticians, education classes, or other appropriate resources offered at KPCO. Primary care providers will be informed of all medication initiations or dosage adjustments via documentation in the electronic medical record. Any clinical scenarios that the clinical pharmacy specialist is unclear on how to proceed will have requests for consultation of either the PCP, neurologist or the CPCRS medical director. The primary mode of communication between CPCRS and patients will be via telephone or e-mail through kp.org. Patients who achieve their lipid and blood pressure treatment goals will be placed into long-term "CPCRS-maintenance" which will require less intensive CPCRS management. Patients will have laboratories and blood pressure checked annually per regular treatment protocols, until study end.

Usual Care: Patients randomized to Usual Care will continue to receive interventions/procedures they normally receive according to standard/usual care practices.

Follow-up for Laboratories and Blood Pressure Values: The HealthTrac-*Stroke*® disease registry will be used to schedule follow-up contacts in order to minimize the number of subjects lost to follow-up. Letters will be mailed to subjects in the Intervention group reminding him/her to have appropriate laboratories completed, as necessary, using standard CPCRS letters. Patients who fail to have laboratories drawn after 2 mailed reminder letters separated by 1-month will be marked "noncompliant" in the database and receive reminders every 6 months thereafter.

For patients in the Usual Care group, no reminder letters will be sent. However for assessment of lipid and blood pressure control at 3 years (primary outcome)

for both groups, reminder letters will be mailed, if necessary (Appendix VI).

Study end: All patients will be followed for 3 years from randomization or until the first occurrence of KPCO termination date, cardiovascular event, or death.

46.0 Risk Assessment and Mitigation Process (RAMP)

46.1 Check any of the following that are applicable for this research application: Does the study involve the disclosure of KPCO PHI to a collaborator*?

Please click on the help tab to see the new definition of COLLABORATOR

- (•) NO, this study does not require the disclosure of KP PHI to a collaborator. I will inform the IRB of any proposed study modification that will result in sharing KP PHI with a collaborator.
- ( ) YES, This study does require the disclosure of KP PHI to a collaborator in the form of a Limited Data Set (LDS). I understand that the LDS can only include: elements of an address greater than street address; dates of birth; death or service. Prior to disclosure of the LDS, KP will execute a Data Use Agreement with the collaborator. I understand that the use of an LDS mitigates risks to the Participant's privacy and security. I will inform the IRB of any change of disclosure more than a LDS.
- ( ) YES, this study does require the disclosure of KP PHI to a collaborator. I will conduct a thorough and accurate data security risk assessment as required using the RAMP tool. I will indicate all data privacy, security, and confidentiality risks.

47.0 Principal Investigator's Assurance

47.1 The Principal Investigator assures to comply with each of the following statements:

Check each box to indicate your agreement with each statement:

- [x] Accept responsibility for the ethical conduct of the study and the protection of the rights, safety, and welfare of the participants.
- [x] Assure a thorough literature review of risks/benefits has been completed.
- [x] Conduct this study in compliance with the protocol as reviewed and approved by the Institutional Review Board (IRB).
- [x] Accept responsibility that co-investigators and study personnel have appropriate qualifications to conduct this research in accordance with the approved protocol.
- [x] Keep current in training of bioethics and human subjects research and assure all key study personnel are in compliance.
- [x] Use only the currently approved copy of the informed consent to obtain legally effective informed consent from participants, or request a waiver of informed consent as appropriate.
- [x] Keep complete copies of all study records, including all signed participant consent forms and privacy rule authorizations for a period of 6 years after the study has been completed and the IRB has accepted the final report.
- [x] Submit all proposed study changes and obtain prospective IRB approval prior to implementing these changes.
- [x] Submit all personnel changes of Principal Investigator and Co-Investigators to the IRB.
- [x] Report upon discovery all unanticipated problems protocol violations, breaches of confidentiality, or serious adverse events to the IRB. Also report these events as required per study protocol and/or contract agreement to the funding agency, if applicable.
- [x] Submit continuing review reports and/or final reports in a timely manner and in anticipation of the IRB approval expiration date. Failure to comply may result in expiration and/or termination of IRB approval. When a study loses IRB approval, all study activities must stop immediately.
- [x] Arrange for a co-investigator to assume direct responsibility in the event that I am unavailable to direct this research personally. This person should be designated on this application or a modification should be submitted to the IRB to advise them of this change.

- [x] Assure that PHI will be used and disclosed only as described in this application (i.e. PHI will not be re-used or disclosed to any other individual or entity), except as required by law. Any changes to the use or disclosure must be prospectively reviewed by the IRB prior to implementation.
- [x] Assure that I have read the KPCO Conflict of Interest Policies and that I and any individuals who are responsible for the design, conduct or reporting of the research project submitted in this application will abide by these requirements.
- [x] Assure that I have read the KPCO Scientific Misconduct and Responsibilities of the Principal Investigator policies and will abide by these requirements.