1.0 General Information

1.1 *Please enter the full title of your study:

Warfarin Anticoagulation Self-Management: A Pilot Study (WarfSelf)

1.2 *Please enter the Short Study Title:

WarfSelf

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:

Witt, Daniel M

3.2 If applicable, please select the Protocol Staff personnel:

A) Additional Investigators

Clark, Nathan, PharmD
Co-Investigator
Delate, Thomas, PhD, MS
Co-Investigator
Jenner, Kathleen
Co-Investigator
Simmons , Brandon
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:
09/01/2010
Study end date:
01/31/2012

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.)

This study will use the functionality and security features of 'My Health Manager' in KP.org for all communication with patients. Patients will be asked to complete an annonymous post-study questionnaire survey that will not involve any PHI using Survey Monkey.

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?

Only patients with currently active 'My Health Manager' accounts will be recruited, therefore passwords will already have been distributed.

13.2 How will passwords and web access be terminated?

This is not applicable to this study. Patients will retain their passwords to 'My Health Manager' at the completion of the study.

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.)

Existing methods used by 'My Health Manager'

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
Dan Witt	PI	KPCO
Nathan Clark	CO-I	KPCO
Brandon Simmons	CO-I	KPCO
Kathleen Jenner	CO-I	KPCO
Deanna Kurz	PM	KPCO

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

This is the existing system used at KPCO allowing patients and providers to communicate using a secure platform. Study personnel will have access to the data as will the CPAS pharmacists as part of their usual care activities.

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

Mark Groshek

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?

The existing secure 'My Health Manager' system will be used. This system employs the use of secure log-in and password protection and the security of this system is ensured and maintained by existing personnel and infastructure within KP.

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?

The existing secure 'My Health Manager' system will be used. This system has existing authentication processes in place and the security of this system is ensured and maintained by existing personnel and infastructure within KP.

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 study will use the existing and approved system for exchange of information via email between patients and providers. Potential risks to privacy should have been discussed with patients when their 'My Health Manager' account was created and activated. All study data will be presented in aggregate form, individual patients will not be identifiable in any publication arising from this study.

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.

Security controls will be those currently existing in the 'My Health Manager' system.

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)?

Patients will receive their INR results via 'My Health Manger' about 1-4 times per month for the 3 month duration of the study. With each INR, patients will send a secure email to their anticoagulation pharmacist via 'My Health Manager' outlining their plan for their warfarin therapy.

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
Daniel Witt	Principal Investigator	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
Internet Services Group	KP WEB manager	Oakland, CA
Daniel Witt	Principal Investigator	KPCO

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).

Emails will be stored in the usual manner and will be accessible in KP HealthConnect. Data regarding INR dosing and testing dates will be stored in the usual manner in the Dawn AC anticoagulation tracking software application and within KP HealthConnect. All other Study data will be kept behind KP firewall and will be password protected.

29.0 Data Management

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

Not all study data will be restricted to study personnel because INR results and communication with CPAS staff is part of UC as this data is not unique to the study and is used in the routine care of anticoagulated patients and therefore needs to be accessible by health care providers at KPCO. The additional study data that is collected but is not specific to CPAS staff UC for anticoagualted patients and analyzed will be restricted to study staff only. This staff is listed in 29.2 of the application.

29.2 Who will have access to study data?

Name	Title	Affiliation

Dan Witt	PI	KPCO
Nathan Clark	CO-I	KPCO
Thomas Delate	CO-I	KPCO
Brandon Simmons	CO-I	KPCO
Kathleen Jenner	CO-I	KPCO

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

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?

Tom Delate

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.

Background and Rationale:

In patients with atrial fibrillation, venous thrombosis, prosthetic heart valves, and acute myocardial infarction oral vitamin K antagonists, such as warfarin, have been shown in multiple studies to decrease thromboembolic events.[1] Due to the narrow therapeutic window of warfarin, frequent dosage adjustments based on the results of laboratory tests are necessary to optimize therapeutic efficacy (i.e., prevent thrombosis) and minimize the potential for adverse reactions (mainly bleeding).[1] An assessment of coagulation, the international normalized ratio (INR) is used to monitor the effect of warfarin on the hemostatic system.[1] An INR above 2.0 is required to achieve adequate anticoagulation for atrial fibrillation.[2] However, INRs above 4.5 are associated with increased risk of serious bleeding events.[3] Additionally, the anticoagulant effects of warfarin are patient specific and fluctuate as a result of interactions with a large number of other drugs, foods, and herbal agents, as well as for no identifiable reason.[1] Therefore, efforts to predict warfarin dosage a priori have been unsuccessful and fastidious dosage individualization is required.[4]

Traditionally the responsibility for adjusting warfarin dose has fallen to either the

patient's physician or specialized anticoagulation management services.[1] Despite best efforts, some patients fail to achieve adequate INR control. In addition, the workload associated with monitoring increasing numbers of anticoagulated patients is exerting pressure on limited healthcare resources. Consequently, alternative methods for managing anticoagulation therapy are being explored.[5]

Patients treated with warfarin are required to take warfarin doses as instructed, adhere to dietary restrictions, and submit to regular blood sampling for INR tests. Anticoagulated patients at Kaiser Permanente Colorado (KPCO) are enrolled in the Clinical Pharmacy Anticoagulation Service (CPAS), a team consisting of Clinical Pharmacists, Clinical Pharmacy Specialists and Pharmacy Technicians with specialized training in anticoagulation therapy management.[6] The INR results in the KPCO system are sent to the managing CPAS pharmacist for assessment and clinical decision making. The patient is then informed of the INR result, the dose of warfarin to take, and the next INR assessment date.

This system has demonstrated effectiveness in improving INR control and reducing the rate of anticoagulation therapy related adverse events, as well as cost effectiveness.[6] However, monitoring anticoagulated patients is labor intensive adding substantial cost to an otherwise low-cost therapeutic intervention. This is especially true for patients with stable INR control that require limited intervention from CPAS staff. While intensive intervention will always be required for complex and non-adherent patients, other models of anticoagulation management for low maintenance patients might benefit both patients and CPAS staff.

Patient self management (PSM) is an alternative model of anticoagulation therapy delivery.[7] In this model, the responsibility for therapeutic decision making is transferred to the patient once PSM competency has been demonstrated. Patients participating in PSM are provided education and tools to help them assume the responsibility for managing therapeutic decisions pertaining to their disease state and healthcare providers remain available to provide assistance and support when needed. PSM has produced favorable outcomes for other disease states including asthma and diabetes with decreases in use of rescue inhalers and improved blood glucose control, respectively.[8;9] The development of point-of-care (POC) devices that allow anticoagulated patients to measure their INRs at home has facilitated similar PSM principles to be applied to warfarin therapy management. Pooled results of randomized, controlled trials of PSM during anticoagulation therapy demonstrate significant reductions in thromboembolic events (OR 0.27, 95% CI 0.12–0.59) and all-cause mortality (OR 0.37, 95% CI 0.16–0.85), but not major bleeding (OR 0.93, 95% CI 0.42–2.05).[10] Self-adjustment of warfarin doses based on INR results in these trials was typically accomplished by providing patients with a pre-determined dosing algorithm.

During the course of therapy, many anticoagulated patients passively acquire a working knowledge of adjusting warfarin doses based on their INR results. This was demonstrated formally in a study showing that even without focused training, patients chose warfarin doses within 2.5 mg per week of the dose recommended by their anticoagulation provider 86% of the time.[11] From this evidence, it is reasonable to conclude that patients who receive formal training should be able to assume responsibility for interpreting their INR result, selecting an appropriate warfarin dose, and determining when to do the next INR test.

While PSM using POC INR monitors appears to improve the therapeutic outcomes of warfarin therapy, the cost and feasibility of this model are barriers to widespread implementation. Obtaining POC INR devices can be cost prohibitive to both patients and

insurers with their costs ranging from $500 to well over $1000 and testing supplies costing approximately $5 per test. These costs may not be covered by health care insurance, whereas the costs of traditional laboratory INR monitoring generally are. Comparatively, the KPCO cost of providing traditional venipuncture INR testing is approximately $1.80 per test. The improved outcomes associated with PSM were derived from RCTs that typically mandated weekly INR testing. This testing frequency is approximately 4-fold higher than is typically required with traditional laboratory INR monitoring. A recent systematic review of RCTs revealed that home POC INR monitoring was 2.4 times more expensive than laboratory monitoring ($667 versus $195 per patient-year).[12] The higher cost of POC testing was driven in part by the higher cost of testing supplies and the increased frequency of INR testing (once per week). In addition to cost constraints, many patients either are not interested in or incapable of PSM using a POC INR monitoring device. Results from clinical trials indicate that for every 100 eligible patients, only 24 would agree to conduct PSM, 17 of those 24 patients could be successfully trained and able to carry out PSM, and only 14 would be able to continue PSM in the long term.[12]

In order to explore the possibility of extending the benefits associated with PSM to more patients without incurring the aforementioned barriers associated with POC INR testing, we propose conducting a prospective pilot investigation of PSM that would leverage the simplicity and low cost of traditional laboratory INR testing with the connectivity associated with the 'My Health Manager' section of the kp.org website. This pilot will entail attempting to enroll a number of eligible patients into a 3-month, one-arm trial of warfarin therapy PSM. The pilot will assess the feasibility of enrolling patients to receive INR results, performed in KPCO laboratories in the usual manner, via email via 'My Health Manager' and then interpret the results, self-adjust warfarin dose(s) via a pre-determined dosing algorithm (when applicable), determine when to retest their INR, and then report this information back to their CPAS pharmacist via email via 'My Health Manager'. The proposed model is unique in that it utilizes INRs obtained via venipuncture, not fingerstick, does not mandate weekly INR testing, and incorporates an existing patient accessible electronic medical record and communication system. Currently, little to no information exists on the reliability, feasibility, or effectiveness of such a PSM model in any healthcare system.

The proposed pilot will provide information on the feasibility of incorporating additional patient participation into warfarin therapy management while maintaining patient safety through ongoing oversight by CPAS pharmacists. In addition, the pilot will provide information on the feasibility of a novel intervention that may reduce the labor intensity of traditional CPAS workflow. As the proposed intervention will target a select group of patients meeting stringent inclusion criteria, it is imperative to evaluate if the investigators can identify a sample of patients capable of participating more actively in their warfarin therapy management. A 100-patient pilot sample is deemed suitable to allow for feasibility assessment of this novel PSM model. If this pilot is successful, a more robust RCT will be developed to further test the proposed PSM model and its effects on patient outcomes.

This proposal aligns with two of KPCO's Strategic Objectives:
Enhanced customer and member engagement
The *WarfSelf* pilot aims to engage anticoagulated members in self-management of a crucial aspect of their health so as to empower them to make informed decisions about their warfarin therapy and at the same time optimize interactions with the healthcare system. In order to eventually conduct a RCT scaled to assess true effectiveness of PSM in this setting, it is important to obtain an accurate estimate of such a program's feasibility.

Consistent adoption of proven care standards and best practices

The *WarfSelf* pilot embraces 'technology that keeps us connected within and outside of KP' at the model's core. The tools employed in this pilot are designed to facilitate communication between patients and providers in an efficient way and results of the pilot may support its processes as a best practice.

Stakeholders and supporters of this pilot in addition to the research team are Dennis K. Helling, PharmD, DSc, FCCP, FASHP, Executive Director, Pharmacy Operations & Therapeutics and Kerstin Froyd, MD Hospitalist & Medical Director of Pharmacy Utilization & Therapeutics.

The intent of this study is that the results will be disseminated via publication of a manuscript summarizing the findings in the peer-reviewed medical literature. In addition, appropriate in-service or other individual or group setting discussions will be conducted at KPCO to disseminate the results among stakeholders

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.

Primary Question:

Can warfarin patients capable of PSM and self-reporting be identified, trained, enrolled and successfully complete a 3-month pilot trial?

Hypothesis: At least 50% of invited patients will provide informed consent and attend a focused PSM training and assessment class

Hypothesis: At least 60% of patients who complete a focused PSM training and assessment class will successfully complete the 3-month pilot trial.

Secondary Questions:

1) Can patient safety be maintained during the pilot?

Hypothesis: The rates of bleeding and thromboembolic complications during the PSM pilot will not exceed historical CPAS rates.

2) Do INR monitoring outcomes differ from pre- to post-pilot?

Hypothesis: Time in therapeutic INR range (TTR) will not decrease and INR testing frequency will not increase from pre- to post-pilot.

3) What characteristics define patients who do and do not successfully complete the pilot?

Hypothesis: Patient characteristics associated with successful pilot completion will be

identifiable and quantifiable.

4) Will patients express a preference for PSM over standard CPAS care?

Hypothesis: At least 50% of enrolled patients will report a preference for PSM over standard CPAS care.

5) Can a focused PSM training and assessment program improve patient's anticoagulation therapy knowledge?

Hypothesis: Average PSM competency quiz scores before vs. after the training program will improve by at least 30%

Objectives:

Primary:
- Develop and refine a focused PSM training and assessment program and patient-friendly warfarin-dosing algorithm
- Identify and enroll approximately 100 patients into a one-arm trial
- Train enrolled patients in PSM
- Complete a 3-month trial of PSM and compare 3-month outcomes of the pilot to outcomes from the 3-month period of time pre-pilot enrollment

Secondary:
- Assess and compare TTR between the study's 3-month pre- and post-periods
- Assess and compare INR testing frequency between the study's 3-month pre- and post-periods
- Assess bleeding and thromboembolic complications in the 3-month post-period
- Describe the characteristics of patients who do and do not successfully complete the pilot
- Describe specific reasons PSM patients return to standard CPAS care
- Assess and compare before vs. after training program average PSM competency quiz scores

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.

Target Population:

The target population will be adult, chronically warfarin-anticoagulated patients enrolled in CPAS. Candidates for PSM will be patients who 1) have a theoretical understanding of oral

anticoagulation and INR monitoring, 2) have been adherent in their INR monitoring (no more than one missed INR test) over the 6 months prior to study enrollment, 3) would be able to interpret the INR in terms of appropriate warfarin dose, 4) have access to a personal computer with active 'My Health Manager' status, and 5) would be able and willing to self-modify their warfarin dose when applicable.

Inclusion criteria:

- Age greater than 18 years
- Indication for warfarin therapy is atrial fibrillation
- Target INR is 2.5 (range 2.0 to 3.0)
- Prescribed 5 mg warfarin tablets at the time of study enrollment
- On warfarin treatment for at least 6 months prior to study enrollment
- Access to a computer with an active 'My Health Manager' account
- Willingness to provide written informed consent

Exclusion criteria:

- Planned surgery/invasive procedure during 3 month pilot
- More than 1 missed INR test during the 6 months prior to study enrollment
- Residing in skilled nursing, assisted living, or long-term care facility
- Planned time away from service area exceeding 7 consecutive days during 3 month pilot
- Pregnant
- Membership gap(s) exceeding 30 days during the 6 months prior to enrollment
- Non-English speaking

Study design:

The study will be a one-arm (i.e., intervention-only), open-label, prospective pilot. Patients will provide written informed consent prior to study enrollment.

Interventions:

Screening, recruitment, & informed consent:

- The CPAS anticoagulation management software will be used to generate a paper list of each pharmacist's atrial fibrillation patients at least 18 years of age, prescribed 5 mg warfarin tablets, and with a target INR of 2.5
    - CPAS pharmacists will use this list and knowledge of their patients to identify those who should not be included in the pilot study (e.g. dementia, lack of adequate family support, alcoholism, etc) and return the list to study personnel. Patients on the list identified as possible candidates will be highlighted by CPAS pharmacists.
    - Study personnel will screen remaining listed patients for study eligibility
    - Patients satisfying initial eligibility criteria screening will receive a recruitment letter (attached) via secure email. ('My Health Manager')
- Study personnel will conduct interviews with interested patients via telephone (see script for recruitment contact), to:
    - Verify eligibility criteria
    - Briefly explain the study and determine if patient is still interested in study participation

- Verbally review the informed consent form (ICF) (see script for recruitment contact), answer questions and determine if patient is willing to provide written informed consent
- Schedule patient for next available study training class (to be held at a selection of KPCO medical office buildings)

- If targeted enrollment is not achieved, study personnel will contact patients via phone who were sent a recruitment letter but did not respond (see script for recruitment contact) and briefly explain the study and determine the patient's interest in study participation
- For interested patients following the outreach call, study personnel will:
  - Verify eligibility criteria
  - Verbally review the ICF, answer questions and determine if patient is willing to provide written informed consent
  - Schedule patient for study training class

Study education & training:

- Weekly study training classes will be scheduled at a geographically diverse selection of KPCO medical office building conference rooms; each class will be able to accommodate between 5 and 20 study patients
- Patients will be provided with a $25 gift check during class check in to defray the costs of study participation (e.g. travel, time away from work, etc)
- During study training classes, patients will:
  - Provide written informed consent and receive copy of ICF
  - Provide HIPAA authorization and receive copy of HIPAA authorization
  - Complete a 10 question pre-education competency quiz
  - Receive verbal and written education and training regarding PSM (including information on patient safety) and study procedures including warfarin dosing decision support tools
  - Complete a 10 question post-education competency quiz

- Post-education competency quiz scores will be reviewed privately with patients at the conclusion of the study training class

  - Patients achieving a score of 70% or more will begin PSM with their next INR test and within 1 week of the study training class
  - Patients achieving a score of less than 70% will conclude participation in the pilot study and continue standard CPAS care
  - Study staff will enter a note in the problems list identifying participation in the PSM study and a study contact number if questions arise.
  - Study staff will also send a staff message to the PCP's informing them of patient study participation.

PSM process:

The duration of PSM will be 3 months from the date of the first study INR

- PSM will consist of the following:
  - Subject will visit a KPCO laboratory for standard INR testing and return home
  - Within 24 hours, subject will receive results of INR testing via 'My Health Manager'
  - Subject will apply knowledge from study training classes and the warfarin dosing decision support tools to determine warfarin dose and date of next INR test
  - Subject will use 'My Health Manager' to email this therapeutic plan using the

standardized format presented during study training classes to their CPAS pharmacist

- CPAS pharmacist will review therapeutic plan
- CPAS pharmacist will document the therapeutic plan in KPHC and the CPAS patient tracking system per standard practice
- In the following circumstances, a CPAS pharmacist may contact a patient via phone or 'My Health Manager' to discuss the therapeutic plan; changes to the plan pursuant to this consultation will be documented in KPHC and the CPAS patient tracking system per standard practice

    - Patient-reported change in warfarin dose (when required) is less than 5% or more than 20% of the previous weekly dose
    - Date of next INR falls outside parameters specified in the study warfarin dosing algorithm

- Missed INR tests will be managed per standard CPAS operating procedure
    - Patients with current and prior stable INR control will be reminded within 10 days of missed INR test via letter or telephone to return for INR testing
    - Patients with current or past unstable INR control or prescribed critical interacting drugs will be reminded within 5 days of missed INR test via telephone to return for INR testing
- Patients will manage potential INR fluctuations caused by changes in diet, alcohol, health status, and/or other medications per the instructions received at study training classes
- Patients with alert INR values (ie >5.0) during business hours will manage their warfarin therapy per the instruction received at study training classes.
- Pateints with alert values outside business hours will be contacted by the CPAS pharmacist on-call. The patient will be instructed to notify the CPAS pharmacist that they are participating in the WarfSelf Pilot Study and will manage their warfarin therapy per the instruction received at study training classes. The on-call CPAS Pharmacist will verify that the patient is not experiencing any bleeding complications as per standard CPAS care.

- Consented patients will be deemed to have completed participation in the PSM pilot and returned to standard CPAS care in the following circumstances:
    - Failure to achieve score of at least 70% on the post-education competency quiz
    - During the 3-month study period:
        - Single INR>10.0
        - Two consecutive INRs greater than 4.5 or less than1.5
        - Hospitalization for a bleeding event or occurrence of a thromboembolic event
        - Failure to return for INR testing after receiving 2 reminders from CPAS staff
        - Patient or patient physician's request
        - Study personnel determine that patient's safety will be compromised by further study participation

- Patients will be surveyed and asked to complete a brief anonymous on-line questionnaire via Survey Monkey® at the end of study participation aimed at assessing:
    - Ways to improve study training classes
    - Satisfaction with PSM
    - Willingness/desire to continue PSM

- Patients will have the option to continue PSM after study completion if: 1) patient would like to continue, 2) patient has demonstated ability to manage warfarin safely, and 3) collaborative decision between patient and CPAS pharmacist is made to continue PSM

Outcome measure(s):
Primary
1) Proportion of potential patients invited to participate actually enrolled in study (i.e., gave informed consent and attended study training class)
2) Proportion of enrolled patients able to achieve at least 70% on the post-education competency quiz
3) Proportion of enrolled patients completing 3 months of PSM

Secondary
1) Rate of anticoagulation-related complications (bleeding, thromboembolism) during study's 3-month post-period will be identified and verified through ongoing medical record review
    - At each INR CPAS staff will review the medical record for complications
    - Bleeding will be defined as the occurrence of a bleeding episode resulting in hospitalization or emergency department visit
    - Thromboembolism will be defined as hospitalization or emergency department visit for objectively confirmed stroke or peripheral embolic event
    - Reporting of bleeding and thromboembolic events will conform to IRB requirements
    - The occurrence of 5 or more bleeding or thromboembolic complications at any point during the study will prompt a safety review of the pilot to determine if it should continue
2) TTR during study's 3-month pre- and post-periods calculated by linear interpolation[13] and reported as a percentage
3) INR testing frequency (INR measurements/90 days) during study's 3-month pre- and post-periods
4) Reasons for return to CPAS standard care
    - Scored less than 70% on post-education competency quiz
    - Single INR greater than 10
    - Two consecutive INRs greater than 4.5 or less than 1.5
    - Occurrence of bleeding or thromboembolism
    - Patient preference
    - Physician preference
    - Other reason(s)
5) Evaluation of satisfaction with PSM and the study training class via post-study survey

6) Contrast the anticoagulation risk factors (hypertension, diabetes, heart failure, prior stroke, prior bleeding, prior thromboembolism), socioeconomic status, percent of INRs in range, and time since anticoagulation inititation) between patients who did and did not enroll in the study.

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.

Analysis:

- This is a pilot study to determine the feasibility of a larger RCT.
  - We estimate that 100 patients will allow us to identify a clinically relevant improvement in pre- and post-period TTR of 10% (65% vs. 75%, respectively), with greater than 80% power at an alpha of 0.05.
- Analyses will be descriptive (e.g., percentages, means, medians)
  - Characteristics of those patients 1) invited to participate, 2) enrolled (provided written informed consent and attended study training class), 3) scoring and not scoring at least 70% on the post-education competency quiz, and 4) able and not able to complete 3 months of self-management will be described and contrasted
  - Characteristics include gender, age at invitation to participate, primary indication for anticoagulation, targeted INR, time interval from initiation of anticoagulation therapy to invitation to participate, and chronic disease score at invitation to participate
- Primary Outcome #1
  - Count of patients enrolled in study will be divided by count of patients invited to participate
- Primary Outcome #2
  - Count of patients achieving at least 70% on the post education competency quiz will be divided by count of patients enrolled
- Primary Outcome #3
  - Count of patients successfully completing 3 months of self-management will be divided by a) count of patients enrolled, b) count of patients achieving at least 70% on the post education competency quiz, and c) count of patients invited to participate

- Secondary Outcome #1
  - Total combined bleeding and thromboembolic complication rate during the 3-month post-period will be calculated by dividing the count of bleeding and thromboembolic events by the total number of patient-years accumulated by patients participating in PSM
  - Separate rates will also be calculated for bleeding and thromboembolic events
  - Rates during PSM will be assessed against historical CPAS bleeding and thromboembolic rates
- Secondary Outcome #2
  - TTR during the 3 months prior to enrollment will be compared to TTR during the 3 months after PSM commences via paired t-test
  - INR testing frequency (INR/90 days) during the 3 months prior to enrollment will be compared to frequency during the 3 months after PSM commences via paired t-test
- Secondary Outcome #3
  - Reasons for return to CPAS standard care will be tabulated and presented in aggregate

- Secondary Outcome #4
  - Survey results will be tabulated and presented in aggregate
- Secondary Outcome #5
  - Post-education competency quiz scores will be compared to pre-education competency quiz scores via paired t-test

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.

Risks
Due to the narrow therapeutic window of warfarin, frequent dosage adjustments based on the results of laboratory tests are necessary to optimize therapeutic efficacy (i.e., prevent thrombosis) and minimize the potential for adverse reactions (mainly bleeding). Patients in this study will continue to be exposed to the risks of warfarin therapy. In addition, patients will be making independent decisions about adjustments in their warfarin therapy and are at risk for making mistakes in judgment that could result in bleeding or thrombosis. Results from previous studies of warfarin PSM have shown that the risk of these adverse events are usually decreased with PSM. The risk of dosing mistakes will also be minimized by the fact that each patient decision will be reviewed by anticoagulation service pharmacists who will intervene when patient decisions fall outside established parameters.

Risks to patient confidentiality should be no greater than what is experienced in usual patient care as existing information systems (HealthConnect, Dawn AC, 'My Health Manager') are being used in this study.

Benefits
Pooled results of randomized, controlled trials of PSM during anticoagulation therapy demonstrate significant reductions in thromboembolic events and all-cause mortality. The proposed pilot will also provide information on the feasibility of incorporating additional patient participation into warfarin therapy management while maintaining patient safety through ongoing oversight by anticoagtulation service pharmacists. This novel intervention may reduce the labor intensity of existing workflow allowing anticoagulation service staff to focus on additional high risk patient populations.

Study Alternatives - The patient can continue to receive usual care by the CPAS staff and not participate in the the study.

We do not anticipate any risks to investigators or staff nor do we think this study will be detrimental to KP or KP proprietary information or publication rights. We also do not see any risk for the study data to be misused for non-KP marketing purposes.
The KPCO study team does not have any conflicts of interest with the study.

CPAS staff will be informed of study related activities/events during the course of the study with as needed updates and thru staff meetings via the PI and CO-I, Nathan Clark. Investigators and staff will be informed of study related activities/events during the course of the study via planned study meetings and additional meetings as needed.

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:
100
Total all sites:
100
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:

☑ Consent Form(s)
☑ Authorization Form
☑ Surveys/Questionnaires
☑ Contact/Recruitment Letter
☐ Post Cards
☐ Recruitment Flyer
☑ Phone scripts
☑ Other (Please list below)

37.2 Please list the other participant documents:

Warfarin dosing algorithms
Warfarin therapy management educational material

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)

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

40.0 HIPAA Privacy Rule

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

- [x] 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.
- [x] Waiver of the requirement to obtain HIPAA Privacy Rule authorization to use PHI for participant identification and screening.
- [x] Waiver of the requirement to obtain HIPAA Privacy Rule authorization to use PHI for participant recruitment.
- [ ] Waiver of the requirement to obtain HIPAA Privacy Rule authorization for the entire study.

41.0 HIPAA Privacy Rule

41.1 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

42.0 HIPAA Privacy Rule

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

○ Yes ◉ No

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

Information about patients will be kept confidential and will not be released without their written permission unless compelled by law. All patient identifiers will be removed at the time of data analysis. Patient's identity will not be revealed in any publication or release of results. If a patient decides to participate in this study, they will also be giving consent for the medical research investigator or his/her assistants to review their medical records as may be necessary for this study. All study staff have completed the IRB required training. All files will be kept in a locked area, and all data stored on computers will be accessed by a pass-word protected system only and only by authorized personnel.

42.3 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.

Upon completion of the study and data analysis, all study materials that do not need to be retained for compliance reasons will be promptly discarded or deleted. Study materials required to be retained will be stored as per applicable regulations.

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

Identification and screening of patient eligibility could not be done without the waiver

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

Chart review and access to PHI is necessary to assure patient's meet the study criteria prior to contacting them for possible study participation

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

All patients on the list obtained from Dawn AC, will be screened for eligibility. Only data relevant to study criteria will be used to review for eligibility.

42.7

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):

No PHI will be disclosed. PHI that will be used will be the minimal neccessary to review for inclusion and exclusion criteria.

43.0 Study Procedures

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

Patients will continue to receive the same elements of anticoagulation therapy management they routinely receive from the Clinical Pharmacy Anticoagulation Service with the exception that they will assume reponsibility for making independent decisions about the dosing of warfarin and frequency of INR testing.

Patients will be required to travel once to a KP medical office building conference room to attend a training class, lasting approximately 2 hours, for the purpose of learning how to make independent decisions regarding warfarin dosing and INR testing. At the training class patients will be required to take pre- and post-class quizzes (consisting of 10 short-answer or multiple choice questions) to assess their understanding of warfarin therapy management.

At the end of the 3-month study, patients will be asked to complete a brief annonymous on-line questionnaire. The questionnaire should take no longer than 10 minutes to complete.

Patients will receive their INR results via 'My Health Manager'--this will not be new as patients must have active 'My Health Manager' accounts to participate in the study. Patients will send an email message to their anticoagulation provider via 'My Health Manager' outlining their warfarin therapy plans. This is expected to take approximately 10-15 minutes per INR test. INR will be tested from 1-4 times per month during the 3 month study period.

Patient outcomes will not be linked to provider behavior.

Participation will be documented in the participant's medical record.

Patients will continue to receive the same tablet strength of commercially available warfarin that they were using prior to the study. There will be no special study procedures pertaining to the dispensing of warfarin.

Patients will have blood drawn for INR tests using standard operating procedures.

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

Screening, recruitment, & informed consent:

- The CPAS anticoagulation management software will be used to generate a paper list of each pharmacist's atrial fibrillation patients at least 18 years of age, prescribed 5 mg warfarin tablets, and with a target INR of 2.5
  - CPAS pharmacists will use this list and knowledge of their patients to identify those who should not be included in the pilot study (e.g. dementia, lack of adequate family support, alcoholism, etc) and return the list to study personnel. Patients on the list identified as possible candidates will be highlighted by CPAS pharmacists.
  - Study personnel will screen remaining listed patients for study eligibility
  - Patients satisfying initial eligibility criteria screening will receive a recruitment letter (attached) via US mail or secure email
- Study personnel will conduct interviews with interested patients via telephone (see script for recruitment contact), to:
  - Verify eligibility criteria
  - Briefly explain the study and determine if patient is still interested in study participation
  - Verbally review the informed consent form (ICF) (see script for recruitment contact), answer questions and determine if patient is willing to provide written informed consent
  - Schedule patient for next available study training class (to be held at a selection of KPCO medical office buildings)
- If targeted enrollment is not achieved, study personnel will contact patients via phone who were sent a recruitment letter but did not respond (see script for recruitment contact) and briefly explain the study and determine the patient's interest in study participation

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

For interested patients, study personnel will:
Verify eligibility criteria
Verbally review the ICF, answer questions and determine if patient is willing to provide written informed consent
Answer any questions the pt. may have concerning study participation.
Written informed consent will be obtained at the initial study class (patients will be provided with a copy of ICF).

During training class, HIPAA authorization will be obtained (pateints will be provided with a copy of HIPAA authorization)

Patients will receive a $25 gift card when they attend the training class.

44.0 Risk Assessment and Mitigation Process (RAMP)

44.1 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.

45.0 Principal Investigator's Assurance

45.1 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.

☑ Assure that I have read the KPCO Scientific Misconduct and Responsibilities of the Principal Investigator policies and will abide by these requirements.