Official title: A prospective, randomized study of fixed versus variable dosing of 4-factor prothrombin complex concentrate for emergent warfarin reversal at a large tertiary care medical center

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Study protocol and statistical analysis plan

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Brandon Van Amber, PharmD

Staff Only
Project #
PI:
Submission Date(s):

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A prospective, randomized study of fixed versus variable dosing of 4-factor prothrombin complex concentrate for emergent warfarin reversal at a large tertiary care medical center

****MAIN RESEARCH QUESTIONS, STUDY AIMS, SPECIFIC HYPOTHESES****

1.1 Please clearly state your overall research questions and/or study aims.

Primary Outcome:

1) Is a fixed dose of 4-factor prothrombin complex concentrate (4FPCC) comparable to FDA-approved variable dosing for reversal of warfarin-induced anticoagulation (defined as an international normalized ratio [INR] ≤1.5) in patients with an INR ≥2 experiencing an emergent bleed or requiring emergent surgery?

   Hypothesis: A fixed dose of 4FPCC will be comparable to FDA-approved variable dosing for reversal of warfarin-induced anticoagulation (defined as an international normalized ratio [INR] ≤ 1.5) in patients with an INR ≥2 experiencing an emergent bleed or requiring emergent surgery.

Secondary Outcomes:

1) What is the incidence of a thromboembolic event occurring within 7 days post-reversal with a fixed dose as compared to FDA-approved variable dosing of 4FPCC?

   Hypothesis: The occurrence of a thromboembolic event within 7 days post-administration of a fixed dose of 4FPCC is lower than that of the FDA-approved variable dosing.

2) Does a fixed dose of 4FPCC provide significant cost-savings to the institution in dollars when compared to FDA-approved variable dosing?

   Hypothesis: Utilizing a fixed dose of 4FPCC will provide for significant cost-savings to the institution as compared to FDA-approved variable dosing.

****1. BACKGROUND & SIGNIFICANCE****

1.2 What is the specific knowledge gap that the project intends to fill? Include a brief review of past research in this area, numbering your citations to relevant literature as well as including them in the reference section #9.1.

Warfarin is a common oral anticoagulant utilized in the United States for the treatment and prevention of thromboembolic events and conditions. Although effective, the major complication associated with warfarin is the risk of major bleeding events. Incidence of major bleeding events in long-term warfarin users is 1.5% to 5.2% per year, with mortality exceeding 13%. Among patients with an intracranial bleed, the mortality rate increases to 46%-55% [1]. In these situations, it is imperative to reverse the pharmacologic effects of warfarin quickly in order to minimize bleeding and reduce the risk of death. Warfarin inhibits formation of vitamin K-dependent clotting factors II, VII, IX, X, and proteins C and S. An international normalized ratio (INR) is a commonly utilized laboratory test to measure the amount of anticoagulation

provided by warfarin and is monitored throughout therapy. The INR is a standardized ratio utilizing prothrombin time to prevent variation between institutional laboratories. Prothrombin time is defined as the time required for plasma to clot after addition of clotting factor. A normal INR in a healthy adult can range from 0.8-1.2. The majority of patients on chronic warfarin therapy will have a target INR of 2-3. Some patients may have a target INR slightly different than this therapeutic goal range depending on the indication. An INR <2 may put the patient at an increased risk of thromboembolic events, whereas an INR >3 may have an increased risk of bleeding. Warfarin reversal will need to be considered in patients presenting with a major bleeding event. At Regions Hospital, we consider a warfarin reversal a reversal of the INR to less than 1.5. The products that are approved for warfarin reversal include vitamin K, fresh frozen plasma (FFP), and 4-factor prothrombin complex concentrate (4FPCC). 4FPCC contains all of the vitamin K-dependent clotting factors inhibited by warfarin, making it desirable for use in warfarin reversal for emergent bleeds. Multiple guidelines currently recommend 4FPCC over FFP for warfarin reversal in vitamin K-dependent major bleeding or intracranial hemorrhage [2-5]. 4FPCC has a fast onset of action and has demonstrated significant reversal of INR within 10 minutes. Its duration of action is up to 8 hours, and for this reason it should be given concurrently with vitamin K [6]. Vitamin K has a delayed onset of action due to its need to stimulate the synthesis of clotting factors so its effects begin as the effects of 4FPCC diminish. 4FPCC is the standard of care treatment for this clinical population in the Regions Hospital Emergency Department.

The optimal dose of 4FPCC is currently unknown despite multiple studies evaluating different dosing regimens. The FDA-approved dosing is 25 to 50 IU factor IX per kilogram of body weight, depending on INR. It is dosed to a maximum of 100 kilograms of body weight. The FDA-approved variable dosing algorithm is as follows: initial INR 2-3.9: 25 IU/kg (maximum dose 2500 IU), initial INR 4-6: 35 IU/kg (maximum dose 3500 IU), and initial INR >6: 50 IU/kg (maximum dose 5000 IU) [6]. Exact doses of 4FPCC administered may vary slightly from the calculated doses as the amount of 4FPCC differs based on the vials utilized. There have been studies evaluating the use of fixed doses and variable doses utilizing body weight, body weight in combination with initial INR, body weight in combination with initial and target INR, and physician-chosen doses. Studies utilizing fixed doses or variable doses provided relatively good clinical and INR outcomes. Target INR outcomes were less achievable in studies utilizing physician-chosen doses [7]. Currently, many hospitals, including Regions Hospital, utilize the FDA-approved variable dosing based on body weight and initial INR to guide 4FPCC dosing to reverse warfarin-induced anticoagulation for patients presenting with emergent bleeding or requiring emergent surgery while on warfarin anticoagulation therapy. The FDA-approved dosing strategy is efficacious; however, its cost is significant to an institution. There were 67 cases of 4FPCC administration between January 2015 and May 2016 at Regions Hospital. The mean dose administered was 3021 IU (range 1000 IU to 7000 IU) and the average cost was $7,236.17 (range $2530 to $17710) per dose... If clinically effective, a lower dosing strategy by means of a fixed dose may cost less than the FDA-approved variable dose. The lack of prospective studies evaluating fixed dosing regimens, especially in the United States, has hampered the emergence of fixed dosing as an optimal treatment regimen that is more cost effective. By performing a prospective study comparing a fixed dose and the FDA-approved variable dose, fixed dosing may be comparable to the FDA-approved dosing in emergent warfarin reversal. This could provide significant cost-savings to institutions and benefit patients in need of emergent anticoagulation.

Previous retrospective studies evaluating fixed doses of 500, 1000, and 1500 IU of 4FPCC demonstrated adequate warfarin reversal. Target INR values of less than 2 and 1.5 were utilized in the majority of studies and were achieved in more than 90% of patients when a 1000 or 1500 IU dose was used [8-11]. A systematic review of 28 studies demonstrated the fixed 4FPCC doses have similar efficacy when compared to variable doses [7]. A retrospective study published in 2015 and performed at Hennepin County Medical Center (HCMC) in Minneapolis, Minnesota analyzed the results after implementation of a 1500 IU fixed dose protocol. This regimen differs from many European studies that demonstrated relative efficacy at 500 and 1000 IU fixed doses. The 1500 IU fixed dose was chosen due to the larger obese population in the United States. Their findings suggest that a fixed 1500 IU dose is sufficient to provide adequate warfarin reversal, as a target INR of less than 2 was obtained in 92.3% of patients and 71.8% of patients achieved an INR less than 1.5 [11]. The primary issue preventing widespread implementation of a fixed dose of 4FPCC is the lack of studies directly comparing a fixed dose to a variable dose, FDA-recommended dosing strategy. Furthermore, the relevant studies have been retrospective, with the exception of one prospective study, which was performed in the Netherlands, providing little generalizability to the United States population.

1.3 What preliminary results do you have that support your proposal?

Currently, Regions Hospital utilizes the FDA-approved variable dosing for 4FPCC administration. There were 67 cases of 4FPCC administration between January 2015 and May 2016 at Regions Hospital and the mean dose administered was 3021 IU (range 1000 IU to 7000 IU). On average, the cost was $7,236.17 (range $2530 to $17710) per dose. This mean dose is much higher when compared to studies that have utilized lower fixed doses and demonstrated adequate warfarin reversal. This may demonstrate that we are over-administering clotting factors when a lower fixed dose will be sufficient. Regions Hospital will be participating in a prospective study evaluating the use of a fixed dose of 4FPCC compared to the FDA-approved variable dose.

An observational cohort study published in 2011 demonstrated comparable efficacy between fixed dosing and variable dosing. The study examined three target INRs (<1.5, <1.8, and <2) depending on indication. Patients received 4FPCC as either a 1040 IU fixed dose or package-insert variable dosing. The median dose for patients in the variable dose cohort

was 1560 IU. Target INR was achieved in 70% of patients receiving a fixed dose and 81% with variable dosing [9]. Even though this finding was not significant, fixed dosing demonstrated a trend towards obtaining the INR goal. In addition, successful clinical outcome (bleeding cessation) was similar between the two dosing strategies as 91% of fixed dose patients obtained a successful clinical outcome compared to 94% of variable dose patients.

An observational, prospective, non-inferiority, cohort study published in 2012 compared a 1040 IU fixed dose of 4FPCC to variable dosing. The median dose for patients in the variable dosing cohort was 1560 IU. The study examined a target INR <2 for all indications. The target INR was reached by 91.7% of patients receiving a fixed dose, which was similar to the variable dosing cohort at 94.7% [10]. In addition, the median INR obtained after 4FPCC administration was 1.48 in the fixed dose cohort and 1.4 in the variable dose cohort. A successful clinical outcome (bleeding cessation) was achieved in 96% of fixed dose patients compared to 86% for variable dosing, ultimately demonstrating non-inferiority. Finally, the time to infusion was recorded and found to be significantly lower with the fixed dosing strategy compared to the variable dosing strategy as the median time to infusion was 130 minutes and 160 minutes, respectively. This demonstrates that a fixed dose regimen reduces time to treatment. This study was promising; however, it was performed in the Netherlands making its generalizability to the United States less applicable.

The retrospective study performed at HCMC demonstrated good efficacy for warfarin reversal as indicated by the percentage of patients achieving the INR targets mentioned previously. However, these findings were not compared to a control group. Furthermore, patients receiving a fixed dose had good safety outcomes as no thromboembolic events were reported within 7 days after administration [11]. Finally, significant cost-savings were achieved through the use of a fixed dose of 4FPCC, with a cost avoidance of approximately $40,000 over the study period.

1.4 What is the importance of the research to the scientific community?

By incorporating a fixed dose of 1500 IU, presenting INR and body weight may not need to be determined prior to administration. This may allow for early administration and prevent delay for warfarin reversal in patients with emergent bleeding. This research may determine whether a fixed dose is effective for reversing warfarin to a target INR less than 1.5 compared to FDA-approved variable dosing. In addition, the lower fixed-dose will significantly reduce costs to the institution.

****2. APPROACH****

Some questions in this section do not apply to all study designs; please mark Not Applicable as appropriate.

2.1 Describe the study design (e.g., "This is a randomized controlled trial to test the effect of a guided imagery intervention on sleep quality"). Please see this List of Study Designs.

This is a prospective, randomized trial to determine whether a fixed dose of 4FPCC is comparable to the FDA-approved variable dosing for emergent warfarin reversal.

2.2 How are you identifying eligible subjects or records? (e.g., clinic visit, search of Epic, registry, etc.)

	Not Applicable

The emergency department (ED) research interns and critical care research center (CCRC) research staff will be utilized to identify eligible patients. When a patient presents with an emergent bleed or requiring emergent surgery and is on chronic warfarin anticoagulation requiring 4FPCC use, the physician will notify the ED research intern or CCRC researcher. In addition, the CCRC intern is always in the emergency department and may notice a potentially eligible patient on the ED Track Board in EPIC. The intern would then notify the physician if he or she were not already aware of the patient. The ED research intern or CCRC researcher will then determine whether the patient meets the inclusion and exclusion criteria for the study. If a patient is determined to be eligible and the physician approves enrollment into the study, the CCRC intern will immediately proceed with randomization. Once the patient is randomized, the physician will be notified of the dosing order from the randomization and the physician will place the appropriate order with the IV or ED pharmacist depending on availability. EPIC will have a separate 4FPCC order specific for the research study.

2.3 What is the study population of interest and what are the study inclusion/exclusion criteria?

All adult patients who are on chronic anticoagulation with warfarin and present to Regions Hospital with an INR ≥2 (identified by iSTAT device) experiencing an emergent bleed or requiring emergent surgery are eligible for participation in the study. All eligible patients will be screened for the following inclusion and exclusion criteria:

Inclusion Criteria:

- Chronic anticoagulation with warfarin and initial INR ≥2
- Emergent bleeding (i.e. intracranial hemorrhage, gastrointestinal hemorrhage, urgent invasive procedures, etc.) or urgent surgery requiring reversal of INR to ≤1.5

Exclusion Criteria:

- Younger than 18 years of age
- History of heparin-induced thrombocytopenia (HIT)
- Patients without initial or post-administration INR readings
- Patients with an initial INR <2
- Pregnant patients
- Prisoners

2.4 If you are not using the entire population of interest, what is the method for obtaining a subset or sample of this population?

X	**Not Applicable**

2.5 Will you need to perform "preparation for research" activities prior to consenting subjects for research?

	No
	Yes
x	**Not Applicable**

If you answered yes above, appropriate preparation for research activities prior to consenting subjects must include the following process to determine inclusion/exclusion criteria:

1) Study staff will work with the PI to determine the methods used in identifying potential subjects for the research. For example, this may include creating an Epic Workbench report of patients who are in the hospital and meet minimum criteria for the research.

2) Study staff may access medical records of all potential subjects' identified (i.e., Workbench) to determine eligibility criteria using information that already exists in the medical record. During this process, no identifiable information may be recorded and any documentation made of a potential subject's information that would disqualify them will be destroyed.

   If an eligible patient is not being cared for by the PI, study staff must approach the patient's provider to determine if it is appropriate to proceed with the consent process.

3) If additional testing needs to be done to see whether a patient meets criteria for entry into the study, the PI or staff will need to consent the patient first.

4) If the preparation activity confirms a patient is a possible subject, PI/staff approaches the patient to begin the consent process.

2.6 Describe the steps in your recruitment process.

	Not Applicable

Screening and Enrollment

The ED research interns and CCRC research staff will be utilized to identify eligible patients. When a patient presents with an emergent bleed or requiring emergent surgery and is on chronic warfarin anticoagulation requiring 4FPCC use, the physician will notify the ED research intern or CCRC staff. The ED research intern or CCRC researcher will determine eligibility and review inclusion and exclusion criteria with the treating physician. In addition, the CCRC intern is always in the emergency department and may notice a potentially eligible patient on the ED Track Board in EPIC. The intern would then notify the physician if he or she were not already aware of the patient. If a patient is determined to be eligible and the physician approves enrollment into the study, the CCRC intern will immediately proceed with randomization. Once the patient is randomized, the physician will be notified of the dosing order from the randomization and the physician will place the appropriate order. Due to the emergent nature of this condition, randomization envelopes will be in a locked area in the Emergency Department in order to expedite randomization and not impede urgent treatment.

Following randomization, the patient will either receive either a fixed or variable dose of 4FPCC per study protocol.

CCRC interns will abstract the study data points from the patient's EMR while the patient is in the Emergency Department

and again at the time of discharge. The variables listed on the attached data collection form will be incorporated into a secure RedCap database that the interns will use to enter the data. All patients will be identified in RedCap with a study ID number that is not linked to identifying information in the database.

Randomization

Given the emergent nature of need for care with this clinical population, randomization will need to happen quickly following the physician decision to use 4FPCC for bleeding reversal. The CCRC intern is in the emergency department 24/7 and is able to respond quickly to the needs of patients upon physician request. This study will utilize a permuted block randomization schedule to allow for equal allocation of subjects in each arm. Given that we expect to enroll 4 patients per month over a 1-year time period, allowing for a total sample size of 48 patients (24 per group), the randomization scheme will consist of 12 permuted blocks of four. Sealed envelopes with the dosing arm (fixed vs. weight-based) will be in the research file in the locked medication room located in Pod E. Pod E is the area of the emergency department reserved for the most acute patients and is where these patients will be treated. All interns have badge access to the medication room. A filing box containing documents specific to ED research is located in the medication room. Once the treating physician deems a patient eligible, the intern will retrieve the envelope from the medication room; open the envelope and the physician will enter the order. We do not anticipate that randomization will take more than 20-30 seconds and thus will not delay patient care or treatment.

Staff Training

CCRC Intern Group
Dr. Van Amber will train the CCRC intern group at the monthly intern dinner in January 2016. Training will involve a PowerPoint presentation reviewing the background and significance of this study as well as the aims and hypotheses. The interns will be trained on the full study protocol with emphasis on the inclusion and exclusion criteria. Dr. Van Amber will also review a mock patient for data abstraction to ensure that everyone is getting data points in the EMR from the same location. Ms. Wewerka will train interns on the randomization procedure.

ED Staff Training

- All attending physicians will be informed of the study at the monthly ED faculty meeting in January. Dr. Isenberger will lead this presentation and will answer any questions.
- Residents will be informed of the study during the monthly Resident Rounds in January. This is a monthly 4-hour meeting that is mandatory for all ED residents. Dr. Isenberger attends this meeting and will present the study to the residents.
- ED nursing staff will be informed about the study during daily huddles in the Emergency Department. Huddles are held three times daily for the nursing staff so that all shifts are informed. CCRC staff will attend the huddles to inform nursing staff of the study and answer any questions. We have utilized this method of education in the past and it is the best way in which to reach all nursing staff. We will attend huddles for the two weeks prior to study start.

ED Pharmacy Staff
ED pharmacy staff will be fully trained on the protocol by Dr. Van Amber and Dr. Stoecker. Dr. Stoecker is a senior pharmacist in the emergency department and is the primary investigator on this study. Dr. Van Amber is a PGY-1 Pharmacy Resident at Regions Hospital and is a Co-Investigator on this study. Both Dr. Stoecker and Dr. Van Amber will participate in training the pharmacy group.

2.7 Describe any interventions that are used in this study.

	Not Applicable

Eligible patients will be randomized in a 1:1 fashion to receive either a fixed dose of 1500 IU or the FDA-approved variable dosing based on body weight and presenting INR. The FDA-approved variable dosing algorithm is as follows: initial INR 2-3.9: 25 IU/kg (maximum dose 2500 IU), initial INR 4-6: 35 IU/kg (maximum dose 3500 IU), and initial INR >6: 50 IU/kg (maximum dose 5000 IU). The patient weight will be obtained using a scale and documented by the treating RN. Randomization will be initiated with the research team member notifying the attending physician of patient enrollment, and the physician placing the order that is immediately visible in EPIC to the IV pharmacist preparing the medication. The pharmacist will prepare the study medication as either the fixed or variable dose. Exact doses of 4FPCC administered may vary slightly from the calculated doses as the amount of 4FPCC differs based on the vials utilized. The doses are unable to be blinded by the research team, as the fixed dose will have less drug volume.

Following the randomization to study doses, the patient will be monitored for continued bleeding by the treating physician. If the patient receiving the 1500 IU fixed dose remains in a bleeding state and the INR remains above goal, an additional 500 IU may be administered at the physician's discretion to minimize bleeding and attempt to achieve hemostasis. If a

patient does receive the additional 500 IU dose, the patient will be included in the intent-to-treat (ITT) analysis and considered a treatment failure for fixed dosing. (NOTE: this should be based on INR – not subjective assessment of bleeding)

All patients on chronic anticoagulation with warfarin who present with an emergent bleed or need for urgent surgery will obtain an initial INR value via the iSTAT point of care test and a laboratory INR. Due to urgent need for administration of 4FPCC, the laboratory INR may not be evaluated prior to randomization. After patient enrollment and randomization, the patient will receive the study medication and have a laboratory INR drawn 15 minutes post-administration. Obtaining a pre- and post-INR laboratory value is standard of care in the emergency department. The laboratory INRs will be utilized in all cases to evaluate the change in INR from pre- to post-administration of 4FPCC. The INRs will be collected and documented in the EMR by the treating RN. All patients enrolled in the study will be evaluated and identified via the EMR for development of a thromboembolic event within 7 days post 4FPCC administration. A 7-day follow-up period was chosen based on other studies evaluating a 4FPCC fixed dose [11,12]. Enrolled patients will be prospectively followed throughout admission with daily chart review to determine if a thromboembolic event occurred. The last patient progress note written within the 7-day follow-up period will be evaluated. This will allow us to include all patients who might have been discharged prior to the 7-day period, but were readmitted with a thromboembolic event.

2.8 Provide a brief, sequential, bullet-point description of the all the data collection activities you will conduct from start to finish (e.g., chart review, patient survey, follow-up visits, data pull from the electronic medical record, etc.) and who will conduct each. Please see our Example of Data Collection Steps.

The current study will assess patient data among enrollees for the outcomes presented in section 1.1:

1) Treating physician will notify CCRC intern of potential study patient or the intern will notice the patient on the ED Track Board and notify the physician
2) Patient identification and inclusion/exclusion screening performed by the ED research intern or CCRC researcher
3) Physician approves the enrollment into the study
4) The patient is randomized, the physician orders the randomization dose of study medication and obtains study medication from IV pharmacist
5) Obtain initial INR (this is standard of care, but also a data point used for this study)
6) Obtain post-administration INR 15 minutes after 4FPCC administered (this is standard of care, but also a data point used for this study)
7) Document exact dose of 4FPCC administered
8) Document whether an additional 500 IU dose needed for patient receiving a fixed dose
9) Abstract timing from presentation to 4FPCC administration from EMR
10) Abstract patient demographic information from EMR
11) Complete data entry into study RedCap database
12) Complete follow-up evaluation of thromboembolic events within 7 days post 4FPCC administration
13) Abstract cost of 4FPCC dose administered

2.9 Provide a timeline for the main study activities. Please see our Example Timeline

Milestones	2016				2017												2018				
	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M
- identify ED physician champion	x																				
- develop study protocol	x	x																			
- obtain funding		x	x																		
- IRB approval process		x	x	x	x																
- ED staff (MDs and RNs) and CCRC intern training				x	x																
- enroll patients						x	x	x	x	x	x	x	x	x	x	x					
- statistical analysis																	x	x	x		
- draft publications																			x	x	x

2.10 Describe your plans for ensuring data security

This study involves only minimum necessary data, in which only de-identified data will be reported. Data will be entered and stored in an HP secure RedCap database. All patients in the RedCap database will be identified only by their assigned study ID number. The database linking the patient MRN and ID number will be stored on a password-protected CCRC share drive that is only accessible to CCRC assigned staff. All electronic identifiers will be destroyed from Regions Hospital computers at the time of manuscript completion. There will not be paper data collection records for this study.

2.11. List the KEY variables that will be collected to support the study aims outlined in item 1.1. KEY variables include those used for:

1) achieving the study aims (outcomes, predictors, potential confounders),

2) identifying the study population (for inclusion/exclusion criteria),

3) describing the study population

Please see an Example of a Completed Table and an Example Data Dictionary.

Variable Name	Data Source (patient survey, EMR, claims, registry)	Purpose (sample identification, description, grouping variable, study endpoint, predictor, covariate)	Measurement Scale (binary, continuous)
Presenting INR (iSTAT and laboratory value)	EMR	Study endpoint	Continuous
Time of initial INR draw (iSTAT and laboratory value)	EMR	Variable	Continuous
INR at 15 minutes post-administration of 4FPCC	EMR	Study endpoint	Continuous
Dose of 4FPCC in IU	EMR	Study endpoint	Binary
Time to administration of 4FPCC in minutes	EMR	Study endpoint	Continuous
Administration of additional 4FPCC in fixed dose arm	EMR	Study endpoint	Binary
Thromboembolic events within 7 days	EMR	Study endpoint	Binary
Timing of thromboembolic event	EMR	Study endpoint	Continuous

Patient charge of 4FPCC in dollars	EMR	Study endpoint	Continuous
Institution cost of 4FPCC in dollars (cost per unit)	Biocare	Study endpoint	Continuous
Weight (kg) at presentation	EMR	Covariate	Continuous
Use of other reversal agents (vitamin K and FFP)	EMR	Covariate	Binary
Age	EMR	Covariate	Continuous
Indication for 4FPCC	EMR	Covariate	Binary
Attending Provider Specialty (i.e. emergency medicine, trauma, hematology/oncology, neurosurgery)	EMR	Covariate	Binary
Hospital unit (i.e. emergency department, SICU, MICU, etc.)	EMR	Covariate	Binary
Eligible patients not enrolled due to physician discretion	EMR	Covariate	Binary

2.12 Provide operational definitions of any variables listed above that aren't adequately described by the variable name above, and provide a brief background of any validated measurement scales listed above.

Thromboembolic events may include deep vein thrombosis, pulmonary embolism, ischemic stroke or transient ischemic event, or myocardial infarction.

Indication for 4FPCC may include, but will not be limited to, intracranial hemorrhage, gastrointestinal hemorrhage, ruptured abdominal aortic aneurysm, intrathoracic hemorrhage, spinal cord hemorrhage, neck hematoma, or other emergent surgical indication.

2.13 If you are collecting data elements besides those listed in Table 2.10 above, provide a justification for gathering the additional data.

N/A

Reminder: For chart review studies, a data collection form must be uploaded with your application listing variables collected and how they are recorded (chart review studies). Provided are links to two example chart review tools: **Word Chart Review Example** and **Excel Chart Review Example**

****3. ANALYSIS****

3.1 Describe the statistical methods that will be used to address the study aims. For each aim, this will usually include:

- Description of the sample used for the particular analysis
- The variables included in the specific analysis and their role in the analysis
- Numeric summaries computed (e.g., mean, standard deviation, proportion, correlation)
- A summary of data exploration and presentation activities (e.g., generating scatter plots, summary tables)
- Description of statistical tests (e.g., independent samples t-test, Mann-Whitney test), and models constructed (e.g., logistic regression)

Please see our Examples of Statistical Methods.

Describe here:

Note: Please reference the area/pages of an established protocol if you are not writing your own analysis plan.

The analytic study population will consist of patients enrolled during the study period who meet the inclusion/exclusion criteria in Section 2.3 – namely, adults on long-term warfarin therapy who present to the ED with emergent bleeding, or who are in need of urgent invasive surgical procedures. The exposure of interest will be fixed vs. variable dose 4FPCC, to which eligible patients will be randomly assigned in a 1:1 ratio. To evaluate the success of randomization, we will summarize patient demographics and relevant clinical factors by 4FPCC dosing assignment group, and conduct appropriate statistical tests (Fisher's exact test for categorical variables; Wilcoxon test for continuous variables) to identify any differences in the distributions of these factors. If there are no significant differences ($p<0.05$) found, we will assume successful randomization, and subsequent statistical analyses will not additionally account for covariates.

(Primary) Aim 1: Fixed vs. variable dose 4FPCC and anticoagulation reversal

To evaluate whether fixed dose 4FPCC is acceptably comparable to variable dosing with respect to anticoagulation reversal, as defined by a targeted INR of ≤1.5, we will employ an active-controlled non-inferiority approach to analysis of a randomized trial [D'Agostino 2003]. In order to establish non-inferiority of fixed dosing, we will test the following null and alternative hypotheses:

- H_0: $F - V \leq M$ *(Variable dosing is superior to fixed)*
- H_1: $F - V > M$ *(Fixed dosing is not inferior to variable)*

where V = variable dosing, F = fixed dosing, and M = the non-inferiority margin.

Based on previous literature [D'Agostino 2003, Goldstein 2015] and the available study sample, we propose to set the non-inferiority margin M to -0.1. In other words, if the proportion of warfarin reversal among fixed dose patients is no worse than 10% less than the proportion of warfarin reversal among variable dosed patients, then we will reject the null hypothesis (superiority of variable dosing), and consider the fixed dose to be acceptably non-inferior to variable dosing.

Results to be reported for this aim will consist of the proportion of reversal for each group, the risk difference (RD; the proportion of reversal in fixed group minus the proportion of reversal in variable group), and the risk ratio (RR; the proportion of reversal in fixed group divided by the proportion of reversal in variable group), along with 95% confidence intervals and p-values as appropriate. Non-inferiority will be established if the lower bound of the RD is greater than the pre-specified margin M (-0.1). The primary analysis will use an intent to treat (ITT) approach (fixed vs. variable treatment assignment); however, we will also conduct supplemental analyses using an 'as treated' or 'per protocol' (PP) approach, in which we will compare patients' actual received dose (regardless of assignment) with respect to successful reversal of anticoagulation. We expect the PP approach to complement the primary ITT results, and will be informative particularly if there is non-trivial overlap in dosing by assignment group.

(Secondary) Aim 2: Fixed vs. variable dose 4FPCC and thromboembolic events

Study patients will be followed for 7 days post-administration of 4FPCC for thromboembolic events, as defined in Section 2.12. For this outcome, we will calculate and report the risk (proportion of patients experiencing an event in each group), RD, and RR, with 95% confidence intervals and p-values, as described in Aim 1. While we expect the risk of thromboembolic events to be lower in the fixed dose group, due to the limited number of anticipated thromboembolic events in the study population, the study will not specifically be powered to detect statistically significant differences by dosing group.

(Secondary) Aim 3: Fixed vs. variable dose 4FPCC and costs

Cost outcomes will be assessed for all study patients and compared by dosing assignment. Generalized linear regression models will be constructed to estimate the difference in cost attributable to dosing assignment (β estimate), along with 95% confidence intervals and p-values. Specifications of the statistical models constructed will be dictated by the empirical distribution of cost outcomes, which we anticipate will be non-normal. In this case, the negative binomial distribution or other modeling assumptions may be used as appropriate.

Sample size:

3.2 What is the estimated sample size(s) for the primary study analyses (per group for studies with different arms or comparison groups)?

Preliminary data from Regions Hospital identified 67 patients treated with 4FPCC from January 2015 through May 2016, suggesting that we can expect about 4 eligible patients per month. Thus for a 1-year study we anticipate 48 patients in our study population, with approximately 24 patients in each dosing group. We will request approval to enroll up to 60 patients as more may present to the Emergency Department compared to our historical data.

3.3 The sample size selected was (check all that apply):

X	Based on data likely to be available during a specific time period (often based on data available in past periods)
	To conduct one or more specific analyses with adequate statistical power
	To achieve a specified level of precision in one or more key estimates
	Other (explain):

3.4 Explain your choice of the sample size selection you listed above:

Sample size for this study will directly depend on the number of eligible patients on warfarin who present to the ED with bleeding emergencies during the study period.

3.5 Describe your assumptions concerning data available for analysis (e.g. How many subjects will be randomized, possibly lost to follow-up or a procedure? What do you expect for survey response rates, and how much missing data do you expect?). Include information as it pertains to your study (human or animal).

Our primary assumptions regarding available data include: 1) successful enrollment of eligible patients into the study; 2) complete data collection for relevant study variables; and 3) an even distribution of random assignment (1:1).

Missing data should be minimal, as the relevant clinical measures under evaluation are routinely documented in this context.

We also expect loss to follow-up to be minimal, as the observation period for a given patient is very short (INR can be evaluated within 15 minutes of 4FPCC administration), and it will be unlikely for patients to leave the hospital prior to collection of relevant measures during an emergency care situation. Though it is possible patients may die during hospitalization, sufficient information should be available for these individuals to contribute to the analysis, with the possible exception of Aim 2 (thromboembolic events).

Power analysis

NOTE: If you are doing a descriptive study (i.e., aside from computing confidence intervals you are not using statistical tests, inferential statistical testing for group comparisons, or statistical models), please complete 3.6 and skip 3.7-3.8.

If you are conducting statistical tests, using statistical inference to compare groups, or are building statistical models, please skip 3.6 and complete 3.7-3.8. **Please see our Example Power Analysis.**

3.6 Provide a measure of the precision of your estimates for key study endpoints, (e.g., 95% confidence intervals on proportions or means), using actual expected estimates.

N/A

3.7 What level of differences observed in your primary endpoints would be considered clinically or practically significant?

As dictated by the active-controlled non-inferiority approach, we will consider the fixed dose of 4FPCC to be non-inferior to variable dosing if the proportion of anticoagulation reversal is no worse than the specified difference margin of -10%.

3.8 What is the power for your primary analysis (and the set of assumptions underlying it: hypothesis addressed, expected pattern of effects with justification for these expectations, analysis used, variables in the analysis, effect sizes, sample sizes, alpha level, one or two-sided test)?

Assuming available treatment group samples of N=24, a non-inferiority margin of -0.1, an alpha significance level of 0.05, an expected targeted reversal proportion in the variable dosing group of 0.77 (pooled estimate from 13 previous studies) [Khorsand 2015], and a true difference in proportions of 0, we will have 22% power to detect non-inferiority of fixed vs. variable dosing of 4FPCC.

3.9 What are the limitations of the proposed approach and analysis?

The primary limitation will be low statistical power to reject the null hypothesis (superiority of variable dose 4FPCC), given limited sample size. Additionally, due to the nature of the intervention, blinding of treatment dosage assignment will not be feasible. Finally, patient follow-up for thromboembolic events at 7-days post 4FPCC administration may not be achieved in all patients due to discharge.

3.10 Please name the people who completed the analysis section of this application.

Jeffrey P. Anderson, ScD, MPH

3.11 Please name the people who will summarize data and conduct statistical analysis.

Jeffrey P. Anderson, ScD, MPH, and/or another member of the HealthPartners Institute Research Methodology Group.

****4. RESEARCH TEAM****

List your study team and degrees.	**List what each person will do:** Identify study subjects; Data entry; Chart abstraction; Statistical analysis; Study recruitment; Interview patients; Draft and revise manuscripts	**List each person's experience** Explain each person's previous research experience with the tasks assigned or what other background/experience relates to the task they are assigned.	**Time Estimate** Please estimate the number of hours or % effort each person will spend on the study
Zachary Stoecker, PharmD Principal Investigator	Dr. Stoecker is an Emergency Department pharmacist in the Regions Hospital Emergency Department. He will be responsible for study oversight including oversight of proposal development, training of ED staff, data collection, analysis preparation, and reporting.	Dr. Stoecker has served as a Co-Investigator on other studies in the Regions Hospital Emergency Department. He contributed significant effort to the study design of this project and will be instrumental in training of staff in the emergency department.	10% effort in-kind
Brandon Van Amber, PharmD Co-Investigator	Dr. Van Amber is a PGY-1 Pharmacy Resident at Regions Hospital. He will be responsible for proposal development, assistance with training, data collection, statistical analysis preparation and data validation.	Brandon Van Amber, a PGY-1 Pharmacy Resident at Regions Hospital, will be part of the research team and be using preliminary data as part of his residency research project. Dr. Van Amber will be presenting preliminary results at the Midwest Pharmacy Residency Conference, to the pharmacy staff at Regions Hospital as well as, to the emergency medicine and hematology/oncology departments.	15% effort in-kind and IME Resident Funds
Kurt Isenberger, MD Co-Investigator	Dr. Isenberger is the Director of the Emergency Department at Regions Hospital. He will be responsible for mentoring Dr. Stoecker and Dr. Van Amber and will assist with training of ED attending physicians. He will also assist with the interpretation of the results and manuscript	Dr. Isenberger is the department head of the Regions Hospital Emergency Department. He has served as an investigator on numerous studies in the Emergency Department.	3% effort in-kind

	preparation.		
Casey Woster, MD Co-Investigator	Dr. Woster is a senior attending faculty member in the Emergency Department at Regions Hospital. He will be responsible for mentoring Dr. Stoecker and Dr. Van Amber and will assist with training of ED attending physicians. He will also assist with the interpretation of the results and manuscript preparation.	Dr. Woster has participated in a previous research trial involving a airway management in a simulated difficult airway. He is a staff physician at Regions Hospital in the Emergency Department. He helps teach ultrasound to the EM residents and is in process of becoming a Registered Diagnostic Medical Sonographer.	2% effort in-kind
David Dries, MD Co-Investigator	Dr. Dries is the Director of Surgery Department at Regions Hospital. He will assist with the interpretation of the results and manuscript preparation. He will also serve as a consultant on the project as he has served as an investigator on other anticoagulation studies.	Dr. Dries is the Assistant Medical Director for Surgery of the HealthPartners Medical Group and a Critical Care Surgery staff physician at Regions Hospital. He has served as an investigator on numerous investigator-initiated, industry-funded and federal research trials over the past 20 years.	1% effort in-kind
Robert LeFevere, MD	Dr. LeFevere will assist with patient enrollment in the ED. He will also assist with communications to other ED physicians and manuscript review.	Dr. LeFevere is a senior attending physician in the Regions Hospital Emergency Department. He has participated as an investigator in numerous studies in the emergency department.	2% in-kind effort
Sandi Wewerka, MPH Manager	Ms. Wewerka is the Clinical Research Manager in the Critical Care Research Center. She will be responsible for oversight of CCRC staff and will assist with training and IRB submissions and communications. She will oversee all budget activities.	Experienced pre-hospital researcher; clinical research manager of the CCRC and investigator on numerous studies at Regions Hospital and Regions EMS	5% effort in-kind
Alexia Terwilliger Lead Coordinator	Ms. Terwilliger will be responsible for day-to-day management of the study. She will be responsible for training the intern group on screening, enrollment and data collection. He will confirm data abstraction is being done correctly as per protocol. She will manage all day-to-day aspects of the study and have regular meetings with the investigators.	Ms. Terwilliger is a research coordinator for the Critical Care Research Center. She has extensive experience with patient screening and enrollment, staff training, data collection, data management and patient follow-up.	5% paid effort
Joe Holm, MS Back-up Coordinator	Mr. Holm will serve as a back-up coordinator and will beresponsible for day-to-day management of the study. He will train the intern group (with Dr. Van Amber) on screening, enrollment, consent and data collection. He will assist with signing off the intern group on protocol training.	Mr. Holm is a research coordinator for the Critical Care Research Center. He has extensive experience with patient screening and enrollment, staff training, data collection, data management and patient follow-up. Mr. Holm is a new member of the CCRC staff. He had previously been a study coordinator in the Emergency Department at HCMC.	2% effort paid

CCRC interns Research Assistant	The CCRC Intern group will be responsible for daily screening of eligible patients, consent of patient or family member, data abstraction and data verification. Given the data abstraction responsibilities as well as the screening, consent and enrollment responsibilities.	The CCRC Intern group is trained on protocols in the ED and throughout the hospital. They are housed in the emergency department and are responsible for responding to pages, data collection and data entry.	25% effort paid
Jeffrey Anderson, ScD, MPH Statistician	Dr. Anderson is an epidemiologist in the HealthPartners Institute Research Methodology Group.	Extensive experience in the analysis of observational studies and clinical trials	10% effort paid

****5. DISSEMINATION****

5.1 What are your plans for publication, including target journals?

We plan to publish our results following study completion. The target journals include the American Journal of Emergency Medicine, Thrombosis Research, Hematology, and Journal of Thrombosis and Hemostasis.

5.2 What plans do you have to share results or translate results to care delivery at HP or for HP personnel?

Brandon will be presenting preliminary results at the Midwest Pharmacy Residency Conference, to the pharmacy staff at Regions Hospital as well as, to the emergency medicine and hematology/oncology departments. Our goal is for the data to be incorporated in the development of future policy changes regarding reversal of warfarin anticoagulation.

****6. ENVIRONMENT****

6.1 Where will the study be conducted? Why is the proposed location appropriate for study?

The study will be conducted at Regions Hospital. This location is appropriate as this study is designed to assess the efficacy of fixed versus variable dosing of 4FPCC in emergent warfarin reversal.

6.2 How will the results of this study impact the health of HealthPartners members and the community? Be specific as to whether and how you see any clinical application as a result of this study.

This study has the potential to impact future protocol and prescribing habits of 4FPCC if results show that fixed dosing is as efficacious as variable dosing.

6.3 Does the treatment strategy (drug or service) proposed in the study commit HP to covering or continuing to provide the treatment or program support after the study is completed?

The results of the prospective, randomized study will influence whether Regions Hospital adopts a fixed dosing protocol for 4FPCC administration.

****7. OTHER REVIEW****

7.1 Has this study been submitted for other review and/or received approval/rejection previously, including but not limited to: Federal, collaborative agency, previous HealthPartners (rejected), or other funding sources (e.g., nonprofit foundation review)?

X	**No**
	Yes (Provide dates of submission and status of review [approved, pending, or rejected])

7.2 Does this study require review by HealthPartners Radiation Safety Officer?

X	**No**
	Yes Please state that you have spoken to the Radiation Safety Office (651-254-3322) and have their

	support for this study.

If a research protocol is to involve the use of ionizing or non-ionizing radiation, the principal investigator (PI) should contact the Institutional Radiation Safety Officer (RS0) for Regions Hospital and HealthPartners clinics.
Regions Radiation Safety Office: 651-254-3322.
Frank E. Zink, Ph.D., Radiation Safety Officer for X-Ray Use
Yuanlin Peng, Ph.D., Radiation Safety Officer for Radioactive Materials

****8. DATA ACCESS REQUEST****

These questions must be completed if you are accessing HP/Regions data or if you study involves a HealthPartners Institute programmer. You will need to work with an Institute programmer to complete this form. Please contact Ann Werner (952-967-5263) or Teri Defor (952-967-7304) for assistance.

If you are not proposing the access HP/Regions data (e.g. Animal Study), you may check "N/A" below.

8.1 What is the name of the programmer helped you complete this section?

N/A

8.2 Will you need to add a programmer to your study team?

x	**No**
	Yes

8.3 Considering your inclusion/exclusion criteria described in 2.3, what specific data will you need?

N/A

8.4 What years of data are needed?

Data will be collected prospectively.

8.5 Will any of the study data be shared or transferred to others within HealthPartners?

Only members of the study team will access data.

8.6 Will any study data be shared or transferred to others outside of HealthPartners?

X	**No**
	Yes - mark which method you will use to share study data: [ ] E-transfer [ ] Secure website/portal [ ] Other secure, encrypted method. Describe below.

8.7 Data Sources (please mark all known data sources)

Mark (X)	Data Source	Mark (X)	Data Source
	EWIS – Claims Data		Registries (chronic condition, disease)
	RDW (Research Data Mart) – historical medical, dental, state death data		Inpatient Case Management data (i.e., Care Guide, Care Partner)
	Claims/Mumps/Cache		Paper Medical Chart
X	EPIC (Electronic Medical Record)		Provider's own source (own patient's chart, provider or department/hospital registry)

	EDR (Electronic Dental Record)		Geriatric department data (i.e., transitional, long term care database)
	EDR Reporting		Data directly from contracted clinics
	New Subject Survey		VDW (Virtual Data Warehouse)
	MEDIPAC System (Regions Billing System)		Consolidated Network Provider (CPN)
	Physician Services Department Data		Health Behavior Group Data (e.g., 10,000 steps, HRA)
	MN State Death Data		MN State Birth Data
	Misys/Sunquest (Lab production system)		Clarity (Epic Reporting Database)
	Other (Please describe):		

8.8 Exclusion Lists: Institute programmers are required to review and apply the following privacy requirements to study patients and their wishes regarding access to medical record information.

Mark X	Exclusion List
	HealthPartners Institute Exclusion List which excludes persons from all medical research. This should be used for all studies. Applies to all data used internally and externally.
	Gramm-Leach-Biley Opt-Out List: (if known; sometimes this can be determined after a study starts). Applies to identifiable data being sent externally.
	Consent for Treatment-Payment-Operations (TPO) Opt-Out List: (if known; sometimes this can be determined after a study starts). Applies to identifiable data being sent externally.

8.9 Data Elements (Please mark all elements that will be used/ accessed during the study):

Mark (X)	Data Elements
X	Name
	Address
	Telephone Number (any)
	Fax Number
	Certificate/license number (i.e., DEA number, professional license number)
	Email address
	Device identifier or serial number
	URL or IP address (web addresses)
	Full face photos, biometric identifiers, or other images
	Health Plan beneficiary number (or family contract number)
X	Date of Birth
	Vehicle identification or serial number
X	Medical Record number (or any personal record identifier)

8.10 Data Content (Please mark all content areas that apply to your study

Mark (X)	Data Content
X	Demographic: age and gender

	Health Plan enrollment information (i.e., dates, coverage)
X	Diagnoses - Medical
X	Procedures - Medical
	Mortality Data
X	Lab Results
X	Prescriptions/ Medications
X	Dates of Service (treatment)
X	Facility or Provider Identifier / Characteristics (e.g., specialty, FTE, Clinic)
	Birth Certificate Data
	Pathology / Tissue Type
X	Financial data
X	Provider notes
X	Vitals – height, weight, BP, etc
	Social history – tobacco use, etc.
X	Other Clinical data
X	Other: please describe: the attending physician will be recorded

****9. REFERENCES****

9.1 Please list below or attach a list of numbered references to support your literature review in section 1 above.

1. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124(15):2450-8.
2. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):7S-47S.
3. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032-60.
4. Frontera JA, Lewin iii JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage : A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care. 2016;24(1):6-46.
5. Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011;154(3):311-24.
6. KCENTRA (Prothrombin Complex Concentrate (Human)) [package insert]. Kankakee, IL: CSL Behring; 2014.
7. Khorsand N, Kooistra HA, Van hest RM, Veeger NJ, Meijer K. A systematic review of prothrombin complex concentrate dosing strategies to reverse vitamin K antagonist therapy. Thromb Res. 2015;135(1):9-19.
8. Junagade P, Grace R, Gover P. Fixed dose prothrombin complex concentrate for the reversal of oral anticoagulation therapy. Hematology. 2007;12(5):439-40.
9. Khorsand N, Veeger NJ, Muller M, et al. Fixed versus variable dose of prothrombin complex concentrate for counteracting vitamin K antagonist therapy. Transfus Med. 2011;21(2):116-23.
10. Khorsand N, Veeger NJ, Van hest RM, Ypma PF, Heidt J, Meijer K. An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies. Haematologica. 2012;97(10):1501-6.
11. Klein L, Peters J, Miner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. Am J Emerg Med. 2015;33(9):1213-8.
12. D'Agostino RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. Statist Med 2003; 22:169-86.
13. Goldstein JN, Refaai MA, Milling TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015; 385:2077-87.