Monotherapy Anticoagulation To expedite Home treatment of venous thromboembolism (MATH VTE)

BMS PROTOCOL NUMBER: *CV185-562*

Sponsor: Indiana University

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SYNOPSIS

Observational Study Protocol CV185-562

Protocol Title: Monotherapy Anticoagulation To expedite Home treatment of venous thromboembolism (MATH VTE)

Department: Emergency Medicine

Objective(s): Measure 30 day post diagnosis readmission rate of emergency department patients diagnosed with deep vein thrombosis or pulmonary embolism (venous thromboembolism, VTE) and treated at home with apixaban.

Study Design: Prospective registry

Study Population: Adults with new or recurrent VTE

Data Collection Methods: Patient reported by telephone and medical record review

Data Analyses: Point estimate with 95% confidence interval

Sample Size/Power: N=850 to narrow top limit of 95% CI for proportion of patients readmitted for bleeding or recurrent VTE within 30 days

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1 INTRODUCTION

1.1 Study Rationale

This work seeks to generalize a protocol to improve the transition of care of patients with venous thromboembolism (VTE, including both deep vein thrombosis, DVT, and pulmonary embolism, PE) from the emergency department (ED) to home treatment. We hypothesize a <2% rate of 30 day re-hospitalization for recurrent VTE or bleeding in patients selected as low risk by the modified Hestia criteria or physician discretion and sPESI negative. The 2% upper limit of the 95% CI threshold is justified based upon data from AMPLIFY and pooled data from EINSTEIN DVT and PE which show a point estimate 30 day VTE recurrence rate of 1-1.2%. [1 2] For patients deemed low risk in the present study, it can reasonably be predicted this rate will be considerably lower. The 30 day incidence of major bleeding were <1.0% in both AMPLIFY and EINSTEIN, and for patients with low risk of bleeding, the rate can be expected to be about 0.5% with upper limit 95% CI <1.0%.[3] Additionally, the 90 day incidence of the composite rate for VTE recurrence and major bleeding reported in systematic reviews and meta analyses of outcomes of low risk VTE patients diagnosed in the ED and treated at home with vitamin K antagonists (VKAs) was 18/785 (2.2%, 95% CI 1.4-3.6%).[4,5] Den exter et al randomized 275 Hestia negative patients to be treated with VKAs at home; 90 day follow up found 3 with recurrent VTE and 3 with major bleeding (6/275, 2.2%).[6] Taken together, we submit these data which support the assertion of the upper limit 30 day failure rate (composite of VTE recurrence and bleeding) <2.0% to constitute a reasonable and prudent expectation of standard care. Recent evidence indicates the safety and acceptance of home treatment of both DVT and PE.[7,8] Patient interviews indicate a strong patient preference to this approach over use of injectable low molecular weight heparin and vitamin K antagonists (e.g., https://iu.box.com/riva-patient-interviews). However, clinicians remain reluctant to discharge DVT and PE patients because lack of a "hard wired" system to guarantee patient follow-up[9]. **To help facilitate this transition in care,** in 2013 in Indianapolis, the project leader/principal investigator, implemented an outpatient treatment protocol using target specific anticoagulants (TSA) for patients with VTE in two hospitals with a low risk of treatment failure and drug related side effects. Most importantly, this included two dedicated clinics (known locally as the KLOT clinics) for these patients to follow-up. Two manuscripts describing the outcomes of the first 106 subjects, as well as a case-control cost effectiveness study have been published.[10,11] A third paper documented good patient outcomes and quality of life equal to patients treated with usual care.[9] With more experience, we have found the transition of care can occur from the ED to primary care physicians and even to existing anticoagulation clinics.

Clinicians encounter one low-risk VTE patient who could safely be treated at home in about every 600 patient encounters. [12-15] Systematic reviews and meta-analyses of literature have suggested a <1% failure rate and <1% 30 day bleed rate associated with home treatment of patients with low-risk PE as determined by validated prognostic scores. However, even after careful selection of VTE patients using existing rules, patients have a small probability of an adverse outcome in the short term, helping to fuel clinician desire for a system of patient follow-up. [16,17] The predicate work used the Hestia criteria for both DVT and PE with awareness that Hestia was designed and initially validated for PE patients. Rationale for using Hestia in DVT patients is based upon our survey and in observation of practice; emergency physicians will not discharge DVT patients who fail any of the Hestia criteria. Moreover, in theory because many DVT patients have PE that may be asymptomatic and in absence of pulmonary vascular imaging, clinicians cannot determine which DVT patients have silent PE, the safest option is to screen them as if they have PE[18].

This is a study of implementation and dissemination, conducted with a framework to enhance its value and subsequent adoption.[19] The primary deliverable of this study will be 1. A detailed written protocol, with annotations and unique commentary (i.e. "pearls") by physicians and advanced practitioners who implemented the protocol 2. The outcomes of 850 patients demonstrating the rate of return to the hospital at 30 days. The rationale for 30 days is that in surveys of risk tolerance, 30 days is the most common time duration identified by most emergency physicians as their "responsible" period for the patient.[9,20]

Innovation
This work expands a novel and patient-centered clinical protocol to at least five other states, at least six other independent hospitals, engages primary care physicians, repurposes and integrates existing anticoagulation clinics and provides education and know-how to use urgent care/fast track clinics for follow-up.

This innovative approach will allow generalization of this protocol across the US. Additionally, primary care physicians will be involved and offered education/experience to increase their involvement and acceptance of these patients in follow-up.

For physicians, this work will show a pathway to liberating low-risk patients with VTE from the need for hospitalization. From prior work, these patients make remarkable statements of gratitude, which we believe will translate into high patient satisfaction scores and likelihood to recommend the hospital system to their friends.

1.2 Research Question

Can emergency department patients with acute pulmonary embolism and/or deep vein thrombosis, identified as low risk by objective criteria, be treated at home with monotherapy anticoagulation with an <2% rate of bleeding requiring re-hospitalization or objectively confirmed recurrent VTE requiring re-hospitalization within 30 days.

2 OBJECTIVES

2.1 Primary Objectives

Evaluate the primary effectiveness of an implementation protocol to identify and manage care of patients diagnosed with DVT and/or PE who are discharged from the ED and treated with apixaban. Treatment failure rate, defined as the numerator, comprising the sum of subjects treated in this protocol who are re-hospitalized for >24 hours within 30 days of enrollment for either objectively diagnosed VTE or for major or clinical relevant non-major bleeding related event, divided by the denominator of enrolled subjects. Protocol success will be defined by the upper limit 95% CI for this proportion < 2.0%.

2.2 Secondary Objectives

- Frequency of subject-reported non-major bleeding within 30 days
- Frequency of discontinuation of apixaban in the first month as reported by subject or medical record.
- Total number of days of hospital stay in first 30 days
- Proportion of all subjects with VTE diagnosed in the emergency department treated with protocol

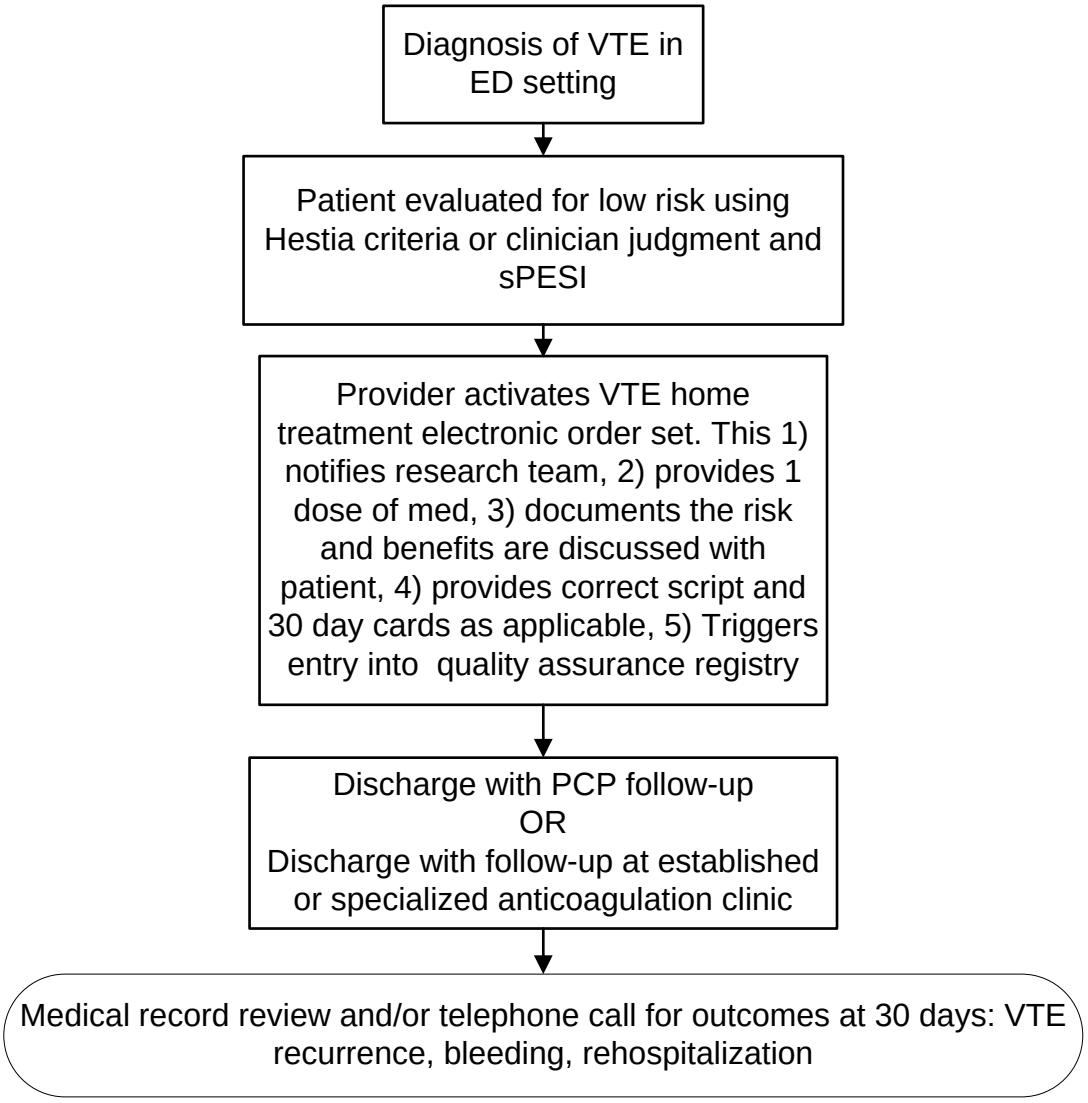
2.3 Exploratory Objectives

Document categorical reasons stated by patient for discontinuation of apixaban, alternative anticoagulation measures used, and rate of discontinuation of the alternative anticoagulant. [Categorical reasons for discontinuation will include: Physician discretion, subject preference without physician oversight, bleeding complication, other suspected medication side effect, financial difficulties with obtaining drug, VTE recurrence on therapy, other reason.]

3 STUDY DESIGN

3.1 Overview of Study Design

Prospective, multicenter observational study, of the effectiveness of a standard of care protocol implemented to enhance home treatment of VTE. Study population will be selected as part of usual care as eligible for home treatment. Study personnel will travel to participating institutions to qualify the sites, deliver a Powerpoint® lecture to introduce the protocol, meet and train site principal investigators, emergency physicians and research personnel on the implementation of the protocol as part of usual clinical care, and data collection methods for a quality assurance registry with plans to use the data collected in this registry in future publications. Follow-up will be 30 days using medical records and/or telephone interview to assess for primary outcomes of bleeding or VTE recurrence.



3.2 Study Population

Emergency department patients with new or recurrent VTE deemed low-risk by modified Hestia or clinician discretion and sPESI (-).

3.2.1 Inclusion Criteria

Criteria for initial VTE diagnosis require a filling defect interpreted as positive on computerized tomographic pulmonary angiography, a ventilation-perfusion lung scan interpreted as high probability, or an incompressible vein observed on venous ultrasound of an extremity or jugular vein. Screening includes electronic surveillance of the "VTE home treatment order set" which ensures low risk criteria and then provides appropriate medication, including apixaban as an option, and discharge instructions. Enrollment occurs at the time of written informed consent.

1. Patients must be **low risk**, as defined by either A or B below:

A. The modified Hestia criteria:

- Systolic blood pressure > 100 mm Hg
- No thrombolysis needed
- No active bleeding
- SaO2 >94% while breathing room air
- Not already anticoagulated
- No more than two doses of IV narcotics in the emergency department
- Other medical or social reasons to admit
- Creatinine clearance >30mL/min
- Not pregnant, severe liver disease or heparin induced thrombocytopenia

OR

B. The physician opinion that a patients' overall social and medical situation is favorable for home treatment and the patient has a zero score on the simplified pulmonary embolism severity index (sPESI).

All of the following must true:

- Age < 81 years
- No history of cancer
- No history of heart failure or chronic lung disease
- Pulse < 110 beats/min
- SBP > 99 mm Hg
- O2 sat >89%%

We have chosen either criteria because both have been found equal in terms of safety for outpatient treatment of PE.[6,22] Hestia includes implicit questions that most emergency physicians would use as criteria for discharge (e.g., overall medical status and social situation), whereas sPESI does not. For that reason, we have added the additional gestalt assessment question about physician discretion.

2. Patients must be discharged in <24 hours after triage in an ED visit with diagnosis of VTE using objective criteria in the emergency department.

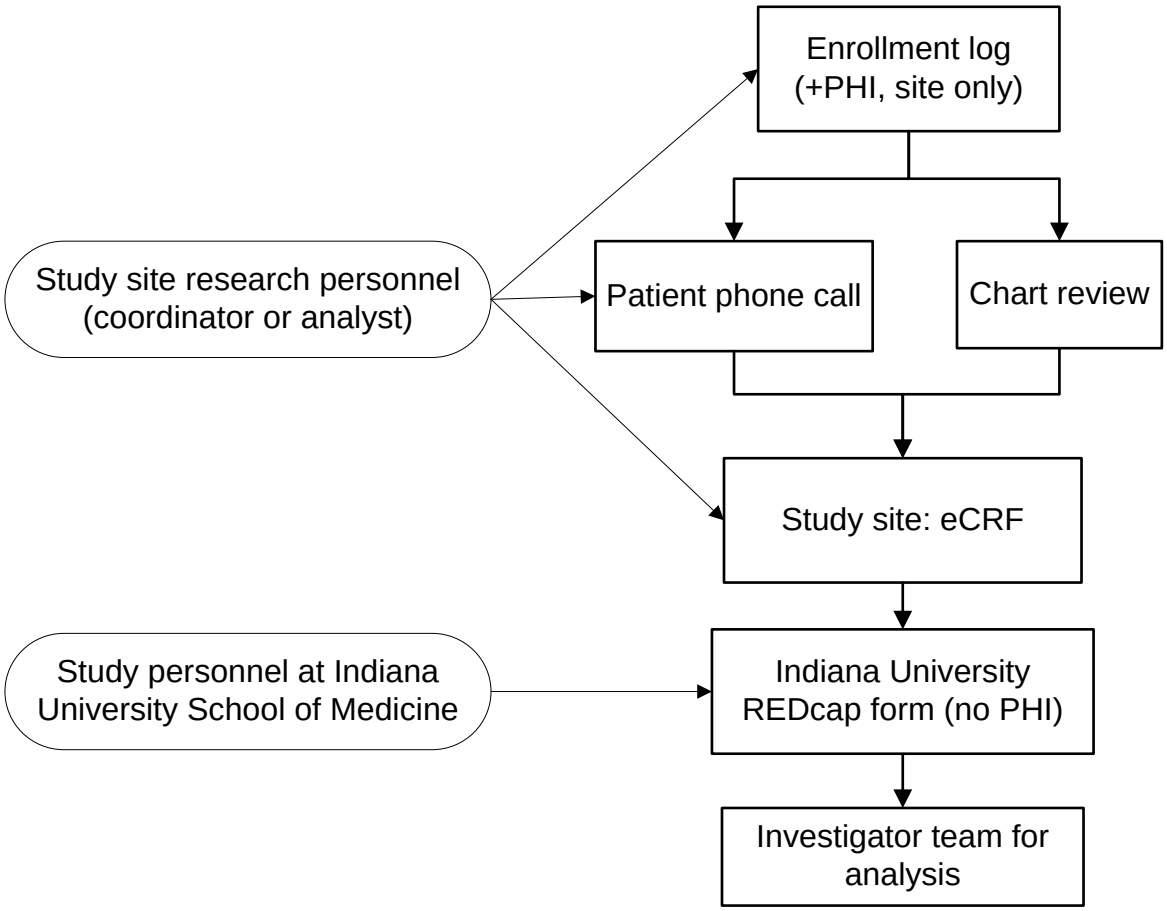
3.2.2 Exclusion Criteria

- VTE diagnosis while taking anticoagulants with evidence of compliance (e.g., physician opinion that patient is taking a Eliquis®, Xarelto® or Pradaxa®, low molecular weight heparin injections or warfarin as prescribed for any condition)
- Sensitivity or contraindication to use of apixaban
- Physician judgment that bleeding risk is high OR Ruiz-Gimenez (RIETE) score >2.[3] https://www.mdcalc.com/riete-score-risk-hemorrhage-pulmonary-embolism-treatment (Note that several criteria are already excluded by Hestia):

  Recent major bleeding, 2 points
  Creatinine levels >1.2 mg/dl, 1.5 points
  Anemia, 1.5 points
  Cancer, 1 point
  Clinically overt PE, 1 point
  Age >75 years, 1 point

3.3 Data Source/Data Collection Process

The figure below demonstrates the data flow process. Each site will complete an electronic case report form that will be linked by a study ID (e.g. CMC001) to the study site enrollment registry, maintained at the study site. The study deliverable is a PHI deidentified REDCap data set (appendix). Placards will be posted in the emergency department with a flow diagram similar to the one diagrammed above. Each site will create a specific "VTE home treatment" order set which prints prescriptions. Subjects will follow-up in designated anticoagulation centers or with a primary care physician. The duration of anticoagulation will usually be at least 3 months.(16) Patients will be identified by query of the electronic order set. Outcomes will be assessed by medical record review and/or a telephone call to each patient made after 30 days after discharge from the emergency department to document outcomes from the time of discharge to 30 days thereafter.



The primary efficacy and safety aims will be assessed by telephone survey and medical record review at or after 30 days, asking the subject explicitly about any change in health status, any unscheduled visit to an emergency department or other healthcare provider, re-hospitalizations, VTE diagnoses, or bleeding events. The script and procedures for the phone call, including handling disconnected numbers, and non-answers will be in the guidance document.

Definitions of recurrent VTE: Study personnel will perform a chart review to confirm suspected recurrent PE/DVT, which will require explicit radiographic or ultrasonic evidence of PE/DVT.

The definition of **re-hospitalization for bleeding** requires chart review demonstrating explicit written decision-making by the admitting emergency physician that a patient was admitted (requiring >24 hour stay) for medical or procedural care to manage objective or suspected bleeding. This would include charted evidence of initially suspected but later disproven bleeding such as gastrointestinal bleeding. Bleeding events will be further characterized as **major bleeding or clinically relevant non-major bleeding**, using published criteria, further defined in the guidance document and using previously established criteria.[3,21]

Secondary objectives

Discontinuation of apixaban. During the follow-up telephone call, patients will be asked if they discontinued apixaban and if so, what anticoagulant they are currently taking.

Capture rate and change in percentage of VTE patients discharged home. The percentage of all VTE (DVT and PE) discharged and change in percentage from pre- to post-implementation will be determined by search of billing records for ICD-10 coding for the immediate 3 months prior to and then 3-6 months after protocol start date.

Exploratory aims

Reason for discontinuing apixaban. Patients will be asked if they are still taking apixaban, and if the answer is no, they will be asked why not and the answer will be documented verbatim. This will be cross-checked by the site PI with the medical record and categorized by the site PI as 1. Bleeding, 2. other side effect, 3. change in diagnosis, 4. new contraindication, 5. patient elected, 6. Physician decision, not otherwise explained, or 7. other

Adverse event investigation. Chart review to investigate possible adverse events will be triggered by subject response to the question about change in health status at the 30 day follow up.

Other publication data for the CRF will be obtained by electronic chart review as previously described.[24]

A PHI stripped eCRF will be populated by study personnel and concatenated with other sites for analysis.

All sites will sign a **data use agreement** that specifies control of data and publication plan.

3.4 Definitions of Study Variables

Recurrent VTE

1. Pulmonary embolism

- a (new) intraluminal filling defect in segmental or more proximal branches on CT,
- a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram,
- a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy.

- inconclusive CT, Pulmonary Angiography, or lung ventilation/perfusion scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography

(Recurrent PE is not diagnosed by CT or ventilation/perfusion scans showing unchanged filling defects compared with the study qualifying images):

OR

2. Suspected (recurrent) DVT with one of the following findings if there were no previous DVT investigations:

- abnormal compression of a deep vein, including calf, gastrocnemius, saphenous vein, femoral, brachial, axillary or jugular veins on ultrasound
- an intraluminal filling defect on venography:

OR

3. Suspected (recurrent) DVT with one of the following findings if there was a DVT investigation at screening:

- abnormal compression ultrasound where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression,
- proximal extension of an intraluminal filling defect, or a new intraluminal filling defect, or proximal extension of non-visualization of veins in the presence of a sudden cut-off on venography

(Recurrent DVT is not diagnosed with compression abnormalities in the same vein as was abnormal on the study qualifying ultrasound).

3.4.1 Outcomes/Endpoint Variables

The primary outcome measures the frequency of one or more episodes of a subject returning for medical care resulting in hospital stay > 24 hours as a direct result of either recurrent VTE or major or clinical relevant non-major bleeding within 30 days of VTE diagnosis that initiated enrollment. For the purpose of this protocol, these events are synonymous with the term treatment failure endpoints. Each case requires medical documentation indicating the reason for hospitalization was for treatment, diagnosis or monitoring of the recurrent VTE or bleeding condition. For example, if a subject returns to an emergency department for chest pain, and reports a nosebleed on the same day, and is hospitalized for testing related to the chest pain, and is not found to have recurrent VTE, the subject does not meet a primary failure endpoint. However, if the subject were admitted for nose packing, or was discovered to have a new PE, then in either case, the subject would meet the primary failure endpoint.

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

Point estimate of the treatment failure rate is (either VTE recurrence or major or clinical relevant non-major bleeding requiring hospitalization) at 30 days with 95% confidence intervals.

4.1.1 Analysis Plan for Primary Objective

The primary effectiveness aim will be calculated by determining the treatment failure rate, defined as the numerator of subjects treated in this protocol who are re-hospitalized for >24 hours within 30 days

of enrollment for either objectively diagnosed VTE or for major or clinical relevant non-major bleeding related event, divided by the denominator of enrolled subjects. The primary analysis is descriptive, using the 95% CI from the exact binomial formula.

Effectiveness success is defined as the upper limit of the 95% confidence interval from the proportion with treatment failure within 30 days exact binomial calculation <2% rate of re-hospitalization for recurrent VTE or bleeding.

4.1.2 Analysis Plan for Secondary Objectives

Descriptive statistics with 95% confidence intervals where appropriate.

4.1.3 Analysis Plan for Exploratory Objectives

Descriptive statistics with 95% confidence intervals where appropriate with comparison of proportions (e.g. proportion of VTE patients treated at home pre vs. post implementation) using 95% confidence intervals for difference in proportions.

4.2 Power/Sample Size

For the primary effectiveness endpoint (rate of hospitalization >24 hours for VTE recurrence or bleeding, also known as a failure rate) within 30 days, with the top limit 95% CI <2.0%. The following table shows the top limit of the 95% CI for various assumptions with a **denominator (sample size) of N=850**:Number of failures	Upper limit 95% CI
0	0.4
1	0.1
2	**0.8**
3	**1.0**
5	1.2
6	1.5
7	1.6
8	1.8
9	1.9
10	2.0

Preliminary data indicates the feasibility to assume a probable case scenario of 3 VTE recurrences and a worst-case 3 major hemorrhages in the combined VTE group (n=850), allowing for upper limit 95% CI of 2.0 or less.

5 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

5.1 Ethics Committee Review and Informed Consent

The protocol will be implemented as standard of care. Data will be obtained as part of a quality assurance registry, which will be reviewed by each institutional review board for requirements regarding verbal or written informed consent or exemption from IRB review.

5.2 Responsibilities within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with BMS/Pfizer.

5.3 Confidentiality of Study Data

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

For the purposes of protecting a patient's identity, a unique code will be assigned to each patient, such as a series of numbers and/or letters (for example, CMC001). The data that is recorded with the patient's assigned code is called “key-coded data”. Key-coded, deidentified study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the “REDCap study database”). Only the site personnel can link between subject’s study ID and the subject’s PHI. However, in case of an audit or inspection, subject to local laws and regulations, government officials, IRB/EC representatives and sponsor representatives may access this information at the study site. If the study requires on-site monitoring, subject to local laws and regulations, sponsor representatives will also access the primary data source at the study site (see section 6.4). Data that could directly identify the patient will not be collected in the study database.

5.4 Quality Control

Representatives of Sponsor (IU School of Medicine and Jeffrey Kline) and/or its delegates must be allowed to visit all study site locations to assess the data quality and study integrity. On site, they will review study files and, if allowed by local laws and regulations, patient medical charts to compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by sponsor internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Sponsor audit reports will be kept confidential.

The investigator must notify Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor.

CRFs will be checked by a trained study analyst for completeness and sensibility of data entries, including obviously out of range parametric values (e.g, age entered as “811”) or non-responsive entries (e.g. “N/A”, unk., n.d.). After initial verification, the analyst will send queries to sites to resolve missing or nonsensical data. Data will be single entered by one analyst. All entries will be verified by the source CRF, signed by the site PI.

5.5 Database Retention and Archiving of Study Documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institutional procedures, for the period specified by the sponsor, or for the period specified by BMS within the project contract, whichever is longer. The investigator must contact Sponsor prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

If the investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, IRB). Notice of such transfer will be given in writing to BMS.

6 ADVERSE EVENT REPORTING

Adverse events will be reported for up to 30 days after enrollment, as triggered by the apixaban home treatment order set. Adverse events discovered primarily based upon the follow-up telephone conversation with subjects and investigated by research personnel and documented on appropriate forms 3500A) and delivered by site personnel under supervision of the site PI as required to the FDA, BMS and if applicable, the local IRB. Adverse events will also be compiled and reported on the CRF including a description of the event, its severity and relatedness.

6.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: Although not always adverse events by regulatory definition, the following events associated with a BMS product must be reported.

- Exposure (to fetus) during pregnancy, exposure (to infant) during lactation, and paternal exposure
- Overdose
- Lack of efficacy
- Abuse
- Misuse
- Off-label use
- Occupational exposure
- Medication error and potential medication error
- Suspected transmission of an infectious agent e.g., any organism, virus or infectious particle pathogenic or non-pathogenic, via the medicinal product.

The causal relationship to the BMS product under study is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between the BMS product under study and the AE.

Not related: There is not a reasonable causal relationship between the BMS product under study and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
A ***non-serious adverse event*** is an AE not classified as serious.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

1. results in death
2. is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. requires inpatient hospitalization or causes prolongation of existing hospitalization (See Note below)
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly/birth defect
6. is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the BMS product under study is an SAE.

An ***overdose*** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events are handled as SAEs.

NOTE:
The following hospitalizations are <u>not</u> considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- elective surgery, planned prior to signing consent.
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy).
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).
- Admission for administration of subsequent anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols).

Adverse Events of Special Interest

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

6.2 Adverse Event Collection and Reporting

Non-serious AEs and SAEs whether or not related to the BMS product under study, pregnancies, AEs associated with maternal exposure, and pregnancy outcomes ascertained in the study must be reported individually in the time frames noted below. All AEs collected will also be reported in aggregate in the final study report.

Any component of a study endpoint that is considered related to study therapy (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE.

6.2.1 Serious Adverse Event Collection and Reporting

Following the subject's willingness to participate in the study, all SAEs, whether or not related to the BMS product under study, must be collected, including those thought to be associated with protocol-specified procedures. SAEs must be reported to BMS (or designee) within 24 hours/1 business day of notification to research personnel to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Although overdose and cancer are not always serious by regulatory definition, these events should be recorded on a form and reported to BMS within 24 hours/1 business day of notification to research personnel.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 1-609-818-3804

If only limited information is initially available, follow-up reports may be required.
For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within **24 hours/1 business day** by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.2.2 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study. Non-serious AE information should also be collected from the start of the observational period intended to establish a baseline status for the subjects.

Non-serious adverse events must be individually reported to BMS (or designee) within **7 business days of notification to research personnel** to comply with regulatory requirements.

All non-serious AEs must be reported by confirmed fax transmission or reported via electronic mail to:

Non-serious AE Email Address: Worldwide.Safety@BMS.com
Non-serious AE Facsimile Number: 1-609-818-3804

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of the BMS product under study and for those present at the end of the study, as appropriate.

6.2.3 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be done every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

7 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

7.1 List of Abbreviations

Term	Definition
AE	Adverse Event
BMS	Bristol-Myers Squibb
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CT	Computed Tomography
DVT	Deep Vein Thrombosis
ED	Emergency Department
EDC	Electronic Data Capture
FDA	Food and Drug Administration
PE	Pulmonary Embolism
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
TSA	Target Specific Anticoagulants
VTE	Venous Thromboembolism

8 REFERENCES

Reference List

(1) Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.

(2) Prins MH, Lensing AW, Bauersachs R et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11:21.

(3) Kline JA, Jimenez D, Courtney DM et al. Comparison of Four Bleeding Risk Scores to Identify Rivaroxaban-treated Patients With Venous Thromboembolism at Low Risk for Major Bleeding. Acad Emerg Med 2016;23:144-150.

(4) Yoo HH, Queluz TH, El DR. Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database Syst Rev 2014;11:CD010019.

(5) Vinson DR, Zehtabchi S, Yealy DM. Can Selected Patients With Newly Diagnosed Pulmonary Embolism Be Safely Treated Without Hospitalization? A Systematic Review. Ann Emerg Med 2012;60:651-662.

(6) den Exter PL, Zondag W, Klok FA et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule With or Without NT-proBNP Testing in Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. Am J Respir Crit Care Med 2016.

(7) Piran S, Le GG, Wells PS et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. Thromb Res 2013;132:515-519.

(8) MacLean S, Mulla S, Akl EA et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e1S-23S.

(9) Kline JA, Kahler ZP, Beam DM. Outpatient treatment of low risk venous thromboembolism with monotherapy oral anticoagulation: patient quality of life outcomes and clinician acceptance. Patient Prefer Adherence 2016;10:561-569.

(10) Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment of low risk venous thromboembolism diagnosed in two U.S. emergency departments with rivaroxaban: A one- year preplanned analysis. Acad Emerg Med 2015;22:788-795.

(11) Kahler ZP, Beam DM, Kline JA. Cost of treating venous thromboembolism with heparin and warfarin versus home treatment with rivaroxaban. Acad Emerg Med 2015;22:796-802.

(12) Feng LB, Pines JM, Yusuf HR, Grosse SD. U.S. trends in computed tomography use and diagnoses in emergency department visits by patients with symptoms suggestive of pulmonary embolism, 2001-2009. Acad Emerg Med 2013;20:1033-1040.

(13) Agency for Healthcare Research and Quality. Information on ED visits from the HCUP Nationwide Emergency Department Sample (NEDS). 2013. 3-21-2015.

Ref Type: Online Source

(14) Beer JH, Burger M, Gretener S, Bernard-Bagattini S, Bounameaux H. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. Journal of Thrombosis & Haemostasis 2003;1:186-187.

(15) Erkens PM, Gandara E, Wells P et al. Safety of outpatient treatment in acute pulmonary embolism. J Thromb Haemost 2010;8:2412-2417.

(16) Vinson DR, Drenten CE, Huang J et al. Impact of Relative Contraindications to Home Management in Emergency Department Patients with Low-Risk Pulmonary Embolism. Ann Am Thorac Soc 2015.

(17) KABRHEL C, Okechukwu I, Hariharan P et al. Factors associated with clinical deterioration shortly after PE. Thorax 2014;69:835-842.

(18) Tzoran I, Saharov G, Brenner B et al. Silent pulmonary embolism in patients with proximal deep vein thrombosis in the lower limbs. J Thromb Haemost 2012;10:564-571.

(19) Neta G, Glasgow RE, Carpenter CR et al. A Framework for Enhancing the Value of Research for Dissemination and Implementation. Am J Public Health 2015;105:49-57.

(20) Than M, Herbert M, Flaws D et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: A clinical survey. Int J Cardiol 2013;166:752-754.

(21) Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-2126.

(22) Jakobsson C, Jimenez D, Gomez V, Zamarro C, Mean M, Aujesky D. Validation of a clinical algorithm to identify low-risk patients with pulmonary embolism. J Thromb Haemost 2010;8:1242-1247.

(23) Kline JA, Jones AE, Shapiro NI et al. Multicenter, randomized trial of quantitative pretest probability to reduce unnecessary medical radiation exposure in emergency department patients with chest pain and dyspnea. Circ Cardiovasc Imaging 2014;7:66-73.

(24) Kline JA, Mitchell AM, Runyon MS, Jones AE, Webb WB. Electronic medical record review as a surrogate to telephone follow-up to establish outcome for diagnostic research studies in the emergency department. Acad Emerg Med 2005;12:1127-1232.

APPENDIX A

Outpatient Treatment Plan

1. Eligibility criteria for discharge from the ED (checkbox

- Modified HESTIA negative
- SBP > 100 mm Hg
- No thrombolysis needed
- No active bleeding
- O2 not required to maintain sats >94% for more than 24h
- Not already anticoagulated
- No severe pain (defined as requiring > 2 doses intravenous narcotics)
- No other medical or social reasons to admit
- Creatinine clearance >30 mL/min
- Not pregnant, no severe liver disease, no history of HIT

OR

sPESI + Physician discretion of absence of other reason for admission adequate social situation and adherence potential, AND

- Age < 80
- No history of cancer
- No history of heart failure or chronic lung disease
- Pulse < 110 beats/min
- SBP > 100 mm Hg
- O2 sat > 90%

Active cancer-Recommend additional screening with the POMPE-C tool.
http://www.mdcalc.com/pompe-c-tool-for-pulmonary-embolism-mortality/n ≤5% mortality risk

2. Labs
CBC and creatinine now

3. Treatment (choose one):

a. Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily for at least three months

i. Give first dose in ED

ii. Don't have to give low molecular weight heparin, but OK to get both

b. Rivaroxaban 15 mg BID for 21 days then 20 mg daily for at least three months

i. Give first dose in ED

ii. Don't have to give low molecular weight heparin, but OK to get both

c. Enoxaparin 1 mg/kg SQ or IV followed by oral anticoagulation of choice for at least three months

4. Discharge instructions