Optimizing the implementation of personalized risk-prediction models for venous thromboembolism among hospitalized adults: The MInimizing RIsk of CLotting Events (MIRICLE) Trial

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Background

There is a critical need for a modern and innovative approach to personalized risk assessment for venous thromboembolism (VTE) among hospitalized adults. VTEs are a significant cause of morbidity and mortality that can be prevented with appropriate and timely initiation of thromboprophylaxis. The annual incidence of VTE is 1–2 per 1000, or 300,000–600,000 events in the United States annually. The VTE attack rate is much higher among currently or recently hospitalized patients compared with those in the general community: 330 versus 8 per 100,000 person-years, respectively. Hospital-acquired VTE (HA-VTE) includes deep vein thrombosis (DVT) and those that travel to the lungs and result in acute pulmonary emboli (PE), which are the most common cause of preventable deaths in the hospital. Despite widespread recognition of the problem and implementation strategies to prevent it, the incidence of VTE has not changed substantially in the last 30 years. The reasons for this lack of progress are complex and not only include the increasing prevalence of contributing factors such as obesity and cancer but also reflect a significant gap in current risk-stratification and prevention strategies.

Acknowledging the increased risk of VTE among hospitalized adults, efforts have focused on VTE prevention during hospitalization. Universal mechanical or pharmacologic prophylaxis increases cost and the potential for harm from the overtreatment of patients at low risk. Numerous prognostic models have therefore been developed to identify those patients with elevated risk of HA-VTE for whom prophylaxis should be considered. A recent systematic review identified several available models and summarized their operational characteristics. Generally, these models are limited to specific patient subpopulations (e.g., patients requiring medical care not in the intensive care unit, patients undergoing surgery), provide overly coarse categories for predicted risk based on dichotomized values for continuous risk factors (e.g., age, body mass index), and are difficult to automate in electronic health record (EHR) systems for use in real time. Unfortunately, most of these models have exhibited modest prediction accuracy in derivation and validation cohorts, resulting in insufficient evidence to recommend the use of any specific model to guide clinical decision making. While clinical practice guidelines recommend some form of risk assessment, many clinicians continue to rely solely on clinical gestalt. The lack of an accurate, flexible, and universal prognostic tool results in variable practice patterns among clinical groups in the same facility and even among practicing partners in the same subspecialty.

We challenge the current paradigm that accurate risk assessment for HA-VTE requires the development and implementation of distinct prognostic models among different patient populations. Although the constellation of predisposing risk factors differs across these patient populations, there is no biological rationale for considering VTE as a different clinical entity among these patient groups. Such a fragmented approach results in models with poor prediction performance and hinders the integration of automated risk assessment into routine clinical practice. Our approach to individualized risk assessment is to develop a single prognostic model in a general patient population and tailor it to individual patients based on their unique combination of risk factors; the model should then be improved and refined over time. Our team has successfully developed a prognostic model for HA-VTE among all adults admitted to Vanderbilt University Medical Center (VUMC). Our model provides granular risk

stratification by calculating the predicted probability of HA-VTE for each patient, maximizes the use of available data by avoiding the arbitrary categorization of continuous variables, and can be automated in EHR systems for use in real time. The model's prediction accuracy is excellent (C statistic: 0.892) and superior to all extant models for HA-VTE.

We acknowledge that, on its own, providing the predicted probability of HA-VTE for each patient will not improve outcomes. User-friendly, understandable, and shareable clinical decision support (CDS) tools are necessary to change provider behaviors and clinical practice. The CDS tool currently in use at VUMC—an OPA (our practice advisory)—is meant to help clinicians order appropriate thromboprophylaxis, but several barriers exist: there is a disconnect between the number of times the OPA 'fires' and the level of harm for HA-VTE; instead of helping clinicians, the OPA is a cognitive interruption in their workflow; and the OPA fires inappropriately at times because it does not take into consideration the full clinical scenario. These barriers provide a ripe environment within which to improve upon and test CDS tools that can lower rates of HA-VTE.

In summary, the current approach for VTE risk assessment is fragmented, insufficiently accurate, challenging for clinicians, and not generalizable. AHRQ identified traits of an ideal VTE prevention protocol; none of these traits are exhibited by extant risk-assessment tools. Our proposed implementation of user-friendly CDS tools based on an automated, real-time prognostic model for HA-VTE that also considers the risk of bleeding complications will exhibit all these traits; we will evaluate whether its use in clinical practice improves patient outcomes in a pragmatic randomized trial.

1.0 Rationale and Specific Aims

In the last 30 years, there has been no significant improvement in rates of venous thromboembolism (VTE). These blood clots develop in the limbs and can travel to the lungs and form pulmonary emboli, which are the most common cause of preventable deaths in the hospital. Currently or recently hospitalized patients account for the majority of VTE cases annually. Failure to recognize and prevent hospital-acquired VTE (HA-VTE) is considered a medical error by the Institute of Medicine. However, the current approach for predicting and preventing HA-VTE among hospitalized adults is not standardized. Clinicians can: order prophylaxis for all patients, thereby potentially harming patients who will not benefit from this intervention; use clinical judgment, which may under- or over-estimate risk and result in medical errors; or apply a risk-stratification tool based on information from the patient history and clinical scenario. Unfortunately, available risk-stratification tools were developed without sufficient input from frontline clinicians, add to clinician workload, are too cumbersome to implement in daily clinical practice, exhibit poor-to-fair prediction accuracy, and do not consider the risk of bleeding complications. Importantly, use of these tools in clinical practice has not been shown to improve patient outcomes. A significant gap therefore exists between the current system of variable practice patterns in VTE risk assessment and the goal of driving down rates of HA-VTE and reducing preventable deaths in the hospital.

Bridging this gap requires implementing an accurate, dynamic prognostic model for development of HA-VTE that is consistently and efficiently used by clinicians. Our research team has developed an automated, real-time prognostic model for HA-VTE among all adult inpatients at Vanderbilt University Medical Center (described in Section

2) based on readily available clinical factors and medical history. The model calculates the probability of HA-VTE, updates as the clinical scenario evolves, discriminates well between high- and low-risk patients, and exhibits superior prediction performance compared with extant risk-stratification tools. In parallel, we conducted observations and interviews with ordering clinicians and nurses (described in Section 2) to ascertain when HA-VTE risk should be assessed, which outcomes should result from implementation of a prognostic model, what the model should include, how and when the model's output should be communicated to clinicians, what clotting versus bleeding risk factors drive prophylaxis decisions, and which implementation strategies will change clinical practice. It is unknown whether use of a prognostic model for HA-VTE in clinical practice improves patient outcomes.

Therefore, we aim to: conduct a pragmatic randomized trial of the automated CDS tools based on a prognostic model for HA-VTE compared with usual care for the prevention of VTE among hospitalized adults. Through an adaptive platform trial, we will evaluate on a prospective basis the effectiveness of model-guided CDS to reduce HA-VTE, both overall and among key patient subgroups, and study through randomization the implementation strategies that work best for clinicians and improve patient outcomes. In a complementary implementation evaluation, we will assess acceptability, appropriateness, and feasibility of the intervention; identify barriers and facilitators to its implementation; and measure its uptake by clinicians in daily clinical practice.

2.0 Animal Studies and Previous Human Studies

Animal Studies: N/A

Observations and Interviews:

In preparation for this clinical trial, we conducted 32 observations and 36 interviews with clinicians across multiple specialties and roles (physicians, pharmacists, nurses, physician assistants, nurse practitioners, and medical residents) to gain an understanding of current VTE risk practices at Vanderbilt Adult Hospital and receive feedback on the initial prognostic model previously developed. These interviews guided refinement of the prognostic model, including variable selection. Observations and interviews were completed as part of a related IRB study (IRB #240579). Deidentified data of observations and interviews may be accessed throughout the course of this study.

Clinicians also had the opportunity to provide additional feedback through two design workshops, conducted with the Center for Research and Innovation in Systems Safety (CRISS). Clinician feedback on visualization and implementation strategies helped inform the creation of user-friendly CDS tools that integrate the model into clinical workflows. In this next stage, we plan to test whether the use of the model in routine clinical practice improves patient outcomes.

Model Development and Evaluation:

As part of a related IRB study (IRB #210161), we developed a prognostic model for HA-VTE in a derivation cohort of 132,561 patient encounters at the VUMC adult hospital (1/1/2018–12/31/2020): median age, 56 years, 52.3% female, 16.2% self-report black race, 1214 HA-VTE events (0.9%). Candidate predictor categories included

demographic characteristics and social determinants of health (e.g., age, sex, race, and ethnicity), inpatient encounter details (e.g., admission type), medical history that is either active or diagnosed during the encounter (e.g., Elixhauser comorbidity details, prior history of VTE), vital signs, laboratory measurements, medications (e.g., immunoglobulins, glucocorticoids, statins), nurse-recorded information regarding mobility (e.g., Braden sub-scores, Richmond Agitation-Sedation Scale (RASS) score), and environmental factors (e.g., Neighborhood Atlas's rankings on socioeconomic disadvantage). Presence of HA-VTE between hospital admission and discharge was defined using ICD-10 diagnosis codes. Least absolute shrinkage and selection operator (LASSO) regression with tenfold cross-validation was used for variable selection to select the subgroup of variables minimizing cross-validation error. We used the area under the receiver operating characteristic curve (AUC) as the error measure to be optimized in the cross-validation process. Clinician feedback regarding model complexity and variables necessary for inclusion was also incorporated into the identification of the final prognostic model. Variables selected in the LASSO procedure plus those suggested by clinicians were included in an unpenalized multivariable logistic regression model to formulate the prognostic model.

From the set of 105 potential predictors, the LASSO procedure identified 11 variables (in decreasing order of importance): presence of a central line, oxygen flow, glucocorticoids ordered encounter, fibrinogen, lactate, admission type (elective admissions, through the emergency department, for trauma, interhospital transfer), immunoglobulins ordered during encounter, respiratory rate, Braden mobility sub-score, Braden perception sub-score, and Braden nutrition sub-score. Clinician feedback identified 6 variables: age, sex, coagulopathy comorbidity, blood loss comorbidity, history of cancer, and history of thrombosis. The prediction performance of the resultant logistic regression model with 17 variables was evaluated in a temporal external validation cohort of 171,891 patient encounters at the VUMC adult hospital (1/1/2021–10/21/2024): median age, 56 years, 52.9% female, 15.9% self-report black race, 2230 HA-VTE events (1.3%). The AUC was 0.892 (95% CI: 0.886, 0.897), indicating excellent discrimination accuracy.

3.0 Inclusion/Exclusion Criteria

All adult patients receiving routine inpatient care at Vanderbilt Adult Hospital will be eligible for inclusion in this trial (standard of care dictates that all admitted patient encounters include DVT/VTE prophylaxis set as part of admitting orders).

Inclusion:

- ≥ 18 years of age
- Admitted to an inpatient setting at Vanderbilt Adult Hospital within study period

Exclusion Criteria:

- less than 18 years of age

- Patients under observation status are eligible but will not be subject to randomization unless transitioned to inpatient status. Participation in the trial will end in the case a

patient dies during hospitalization or is converted to hospice care at Vanderbilt Adult Hospital.

4.0 Enrollment/Randomization

Participant screening will be performed using predefined eligibility criteria applied to data contained within the electronic health record (EHR). Eligible patients will be identified through an EHR-based data query developed and maintained by the Vanderbilt Clinical Informatics Center (VCLIC) core team. All adult patients receiving routine inpatient care at VUH will be eligible for inclusion in this trial (standard of care dictates that all admitted patient encounters include DVT/VTE prophylaxis set as part of admitting orders). There will be no active recruitment for the trial. Randomization will occur through a built-in functionality in Epic EHR at the patient level. The clinical decision regarding randomization between the two treatment arms will be arbitrary, meaning randomization will not be based on clinical factors. Patients be treated at VUH for routine care at health system scale. As such, it is not practicable or feasible to actively recruit and consent patients in this dynamic real-world setting. We are seeking a waiver of consent because participation of patients in the trial will not affect their rights or welfare, as both arms will be receiving standard of care (i.e. current workflows for determining risk and ordering of prophylaxis) at minimum.

For patients randomized to the intervention arm, clinical teams will be shown the HA-VTE risk score in their EPIC workflow, and for patients randomized to the control the clinical team will NOT see a risk score but follow standard of care assessment of HA-VTE and prophylaxis per current workflows. Current standard of care dictates that all patients admitted to the inpatient setting at Vanderbilt Adult Hospital are assessed for VTE risk on admission. This risk assessment tools and process differ by service, but all services assess risk as part of their protocols.

Patients under observation status will not be subject to randomization unless transitioned to inpatient status.

5.0 Study Procedures

This is an adaptive platform trial (APT), which is designed to incorporate learning as it occurs and focuses on improving the outcome, rather than on a particular intervention. Intervention components may be modified, removed, or added over time based on predefined decision rules. APTs can yield several important benefits to patients and researchers: components that lack efficacy can be abandoned or replaced; and treatment effects can be estimated with greater statistical precision. We plan to conduct interim analyses every three months to evaluate the intervention and decide on any modifications.

Prediction with Prognostic VTE Model

Our intervention uses a prognostic model for HA-VTE that has undergone temporal external validation at VUMC, as described in Section 2.0. The logistic regression model with 17 variables will be implemented in the CDS intervention(s) in the trial to calculate

a patient's predicted probability of HA-VTE during the encounter. The predicted probability of HA-VTE will be categorized as: <0.01 (or 1%) as "low"; > or = 0.01 (or 1%) to < 0.02 (or 2%) as "elevated"; and > or = 0.02 (or 2%) as "critically high."

Selection and Randomization
We will include all eligible hospitalized adults at VUMC over a 1.5-year period, a defined and inclusive community. Patients will be randomized upon admission using an Epic module.

Primary Outcome
HA-VTE, VTE associated with hospitalization, that occurs after admission. We will exclude VTE present on admission from our study outcomes.

Secondary Outcome
VTE-related visit to VUMC facility (within 90 days post-discharge)

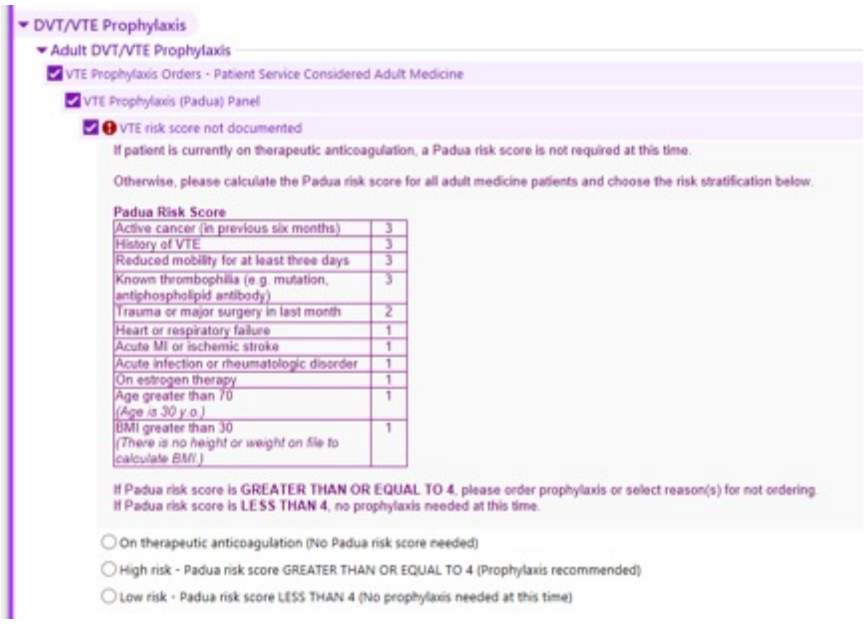
Quality Outcome
Prescription of pharmacological prophylaxis (during hospitalization)
Receipt of non-pharmacological intervention (during hospitalization)

Process Outcome:
Clinician utilization of the CDS tool

Safety Outcome
Major bleeding complications (during hospitalization)

Control
For patients randomized to the control arm, the clinical care team will administer standard of care at VUH and monitor their patients' risk for HA-VTE in accordance with existing protocols and procedures. Standard of care includes assessing patient risk for VTE and initiating prophylaxis if necessary, usually using an order set. If the clinical care team determines that the patient has elevated risk and no contraindications, they will initiate and order prophylaxis using their service line-specific order set and continue to monitor the patient for any complications. Providers caring for patients in the control arm will not be shown the HA-VTE risk score anywhere in the EHR, which is the status quo.

For patients admitted to an Adult Medicine Service, the order set prompts the following calculation of the Padua risk tool for VTE prognostication:

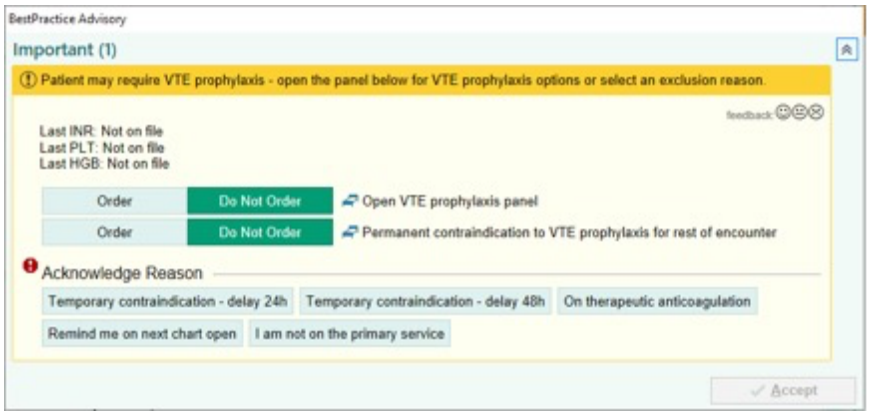


For patients not currently listed as admitted to Adult Medicine, admitting physicians are prompted to indicate if patients will be admitted to Adult Medicine, the service using the DVT/VTE prophylaxis order set:

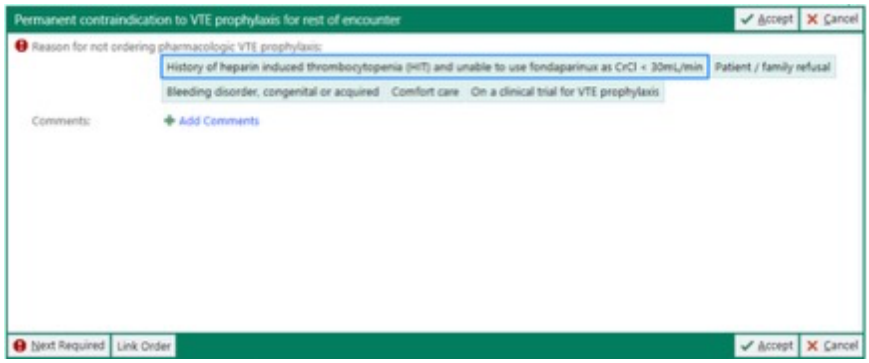


Selecting Yes prompts the Padua risk tool as above.

If the admitting physician selects "High Risk" on the Padua, they are prompted to select prophylaxis through the following OPA:



If they indicate a permanent contraindication "Order", they are prompted to select the reason:



Intervention

Standard of care(i.e., assessing patient risk for VTE and initiating prophylaxis if necessary, usually using an order set) PLUS the % risk of HA-VTE determined from the prognostic model which will automatically calculate a patient's risk score daily based on 17 risk factors. For patients randomized to the intervention, the clinical care team will see the patient's predicted risk score, which will be embedded in their EPIC workflow. The tool may be located in different areas in EPIC based on specialty. The CDS tool will also include a link for clinicians to click-in and explore details about the prognostic model and its risk score calculation, such as contributing factors to the risk score, the logistic regression equation used to calculate the score, how the logistic regression converts to a % risk, the criteria % risk categories for low, elevated , and critically high risk, and a link to a journal publication on the model's development and validation(see below). The clinical care team will have access to review the patient's risk score in conjunction with their clinical judgment to guide decision-making surrounding risk assessment and initiation of prophylaxis (if applicable).

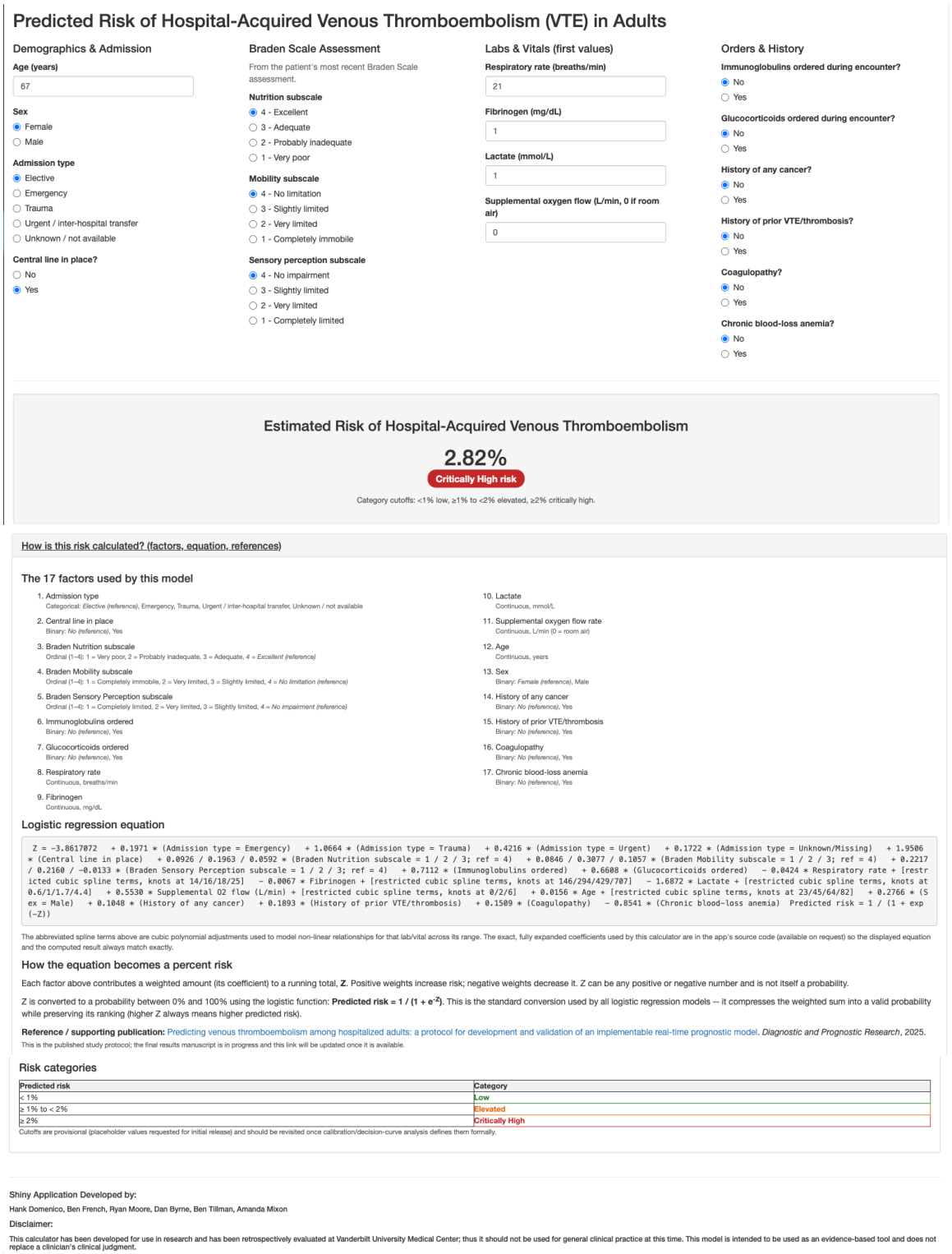
Current availability of tools and protocols vary by specialty. For example, medicine services use the PADUA tool for risk assessment, while nurses use flowsheets to document and assess risk factors. Additionally, current tools such as the PADUA calculate risk on admission but do not recalculate risk based on updated new information during the hospitalization (e.g.vital signs, labs). The intervention will help standardize the risk assessment process by providing a risk assessment tool available across all services that calculates and presents a patient's risk daily. The intervention does not change the risk to the patient nor of the patient in having a HA-VTE. The risk score will not dictate the care of the patient or replace clinical judgment. Rather, it is a tool to further inform clinicians and help guide informed decision-making. Clinicians may choose to ignore the risk score and proceed with their current plan for prophylaxis based on their workflow.

A participant notification sheet would be impracticable to provide to all inpatients. Patients will be unaware of which arm they are randomized to, as the risk score will be presented to the clinical team, and we are determining how the risk score affects their decision on VTE prophylaxis. There would be no advantage to the patient to be in the treatment arm vs the control arm, as both arms will receive standard of care. It would not be appropriate to provide patients which arm they are randomized to, as it would affect the integrity of study.

Design:
Because this is an adaptive clinical trial, the display and location of the risk score (the intervention) may change throughout the course of the study based on interim analyses (see attached documents for mock ups of the proposed interventions below). Based on our prior feedback from clinicians, we plan to evaluate the following potential versions of the intervention:

For Ordering Clinicians:
Version 1: The risk score will be embedded in the existing order set for prophylaxis.
Version 2: The risk score will appear in an OPA on the storyboard which will also link to the order set directly.

Clinicians will have the option in the CDS tool to click-in to view more details about the prognostic model using an embedded link. Please see below for information that will be provided to clinicians for further review, if inclined:



Predicted Risk of Hospital-Acquired Venous Thromboembolism (VTE) in Adults

Demographics & Admission

Age (years): 67

Sex
- (•) Female
- ( ) Male

Admission type
- (•) Elective
- ( ) Emergency
- ( ) Trauma
- ( ) Urgent / inter-hospital transfer
- ( ) Unknown / not available

Central line in place?
- ( ) No
- (•) Yes

Braden Scale Assessment

From the patient's most recent Braden Scale assessment.

Nutrition subscale
- (•) 4 - Excellent
- ( ) 3 - Adequate
- ( ) 2 - Probably inadequate
- ( ) 1 - Very poor

Mobility subscale
- (•) 4 - No limitation
- ( ) 3 - Slightly limited
- ( ) 2 - Very limited
- ( ) 1 - Completely immobile

Sensory perception subscale
- (•) 4 - No impairment
- ( ) 3 - Slightly limited
- ( ) 2 - Very limited
- ( ) 1 - Completely limited

Labs & Vitals (first values)

Respiratory rate (breaths/min): 21

Fibrinogen (mg/dL): 1

Lactate (mmol/L): 1

Supplemental oxygen flow (L/min, 0 if room air): 0

Orders & History

Immunoglobulins ordered during encounter?
- (•) No
- ( ) Yes

Glucocorticoids ordered during encounter?
- (•) No
- ( ) Yes

History of any cancer?
- (•) No
- ( ) Yes

History of prior VTE/thrombosis?
- (•) No
- ( ) Yes

Coagulopathy?
- (•) No
- ( ) Yes

Chronic blood-loss anemia?
- (•) No
- ( ) Yes

Estimated Risk of Hospital-Acquired Venous Thromboembolism

2.82%

Critically High risk

Category cutoffs: <1% low, ≥1% to <2% elevated, ≥2% critically high.

How is this risk calculated? (factors, equation, references)

The 17 factors used by this model

1. Admission type
   Categorical: *Elective (reference)*, Emergency, Trauma, Urgent / inter-hospital transfer, Unknown / not available
2. Central line in place
   Binary: *No (reference)*, Yes
3. Braden Nutrition subscale
   Ordinal (1–4): 1 = Very poor, 2 = Probably inadequate, 3 = Adequate, *4 = Excellent (reference)*
4. Braden Mobility subscale
   Ordinal (1–4): 1 = Completely immobile, 2 = Very limited, 3 = Slightly limited, *4 = No limitation (reference)*
5. Braden Sensory Perception subscale
   Ordinal (1–4): 1 = Completely limited, 2 = Very limited, 3 = Slightly limited, *4 = No impairment (reference)*
6. Immunoglobulins ordered
   Binary: *No (reference)*, Yes
7. Glucocorticoids ordered
   Binary: *No (reference)*, Yes
8. Respiratory rate
   Continuous, breaths/min
9. Fibrinogen
   Continuous, mg/dL
10. Lactate
    Continuous, mmol/L
11. Supplemental oxygen flow rate
    Continuous, L/min (0 = room air)
12. Age
    Continuous, years
13. Sex
    Binary: *Female (reference)*, Male
14. History of any cancer
    Binary: *No (reference)*, Yes
15. History of prior VTE/thrombosis
    Binary: *No (reference)*, Yes
16. Coagulopathy
    Binary: *No (reference)*, Yes
17. Chronic blood-loss anemia
    Binary: *No (reference)*, Yes

Logistic regression equation

```
Z = −3.8617072  + 0.1971 * (Admission type = Emergency)  + 1.0664 * (Admission type = Trauma)  + 0.4216 * (Admission type = Urgent)  + 0.1722 * (Admission type = Unknown/Missing)  + 1.9506 * (Central line in place)  + 0.0926 / 0.1963 / 0.0592 * (Braden Nutrition subscale = 1 / 2 / 3; ref = 4)  + 0.0846 / 0.3077 / 0.1057 * (Braden Mobility subscale = 1 / 2 / 3; ref = 4)  + 0.2217 / 0.2160 / −0.0133 * (Braden Sensory Perception subscale = 1 / 2 / 3; ref = 4)  + 0.7112 * (Immunoglobulins ordered)  + 0.6608 * (Glucocorticoids ordered)  − 0.0424 * Respiratory rate + [restricted cubic spline terms, knots at 14/16/18/25]  − 0.0067 * Fibrinogen + [restricted cubic spline terms, knots at 146/294/429/707]  − 1.6872 * Lactate + [restricted cubic spline terms, knots at 0.6/1/1.7/4.4]  + 0.5530 * Supplemental O2 flow (L/min) + [restricted cubic spline terms, knots at 0/2/6]  + 0.0156 * Age + [restricted cubic spline terms, knots at 23/45/64/82]  + 0.2766 * (Sex = Male)  + 0.1048 * (History of any cancer)  + 0.1893 * (History of prior VTE/thrombosis)  + 0.1509 * (Coagulopathy)  − 0.8541 * (Chronic blood−loss anemia)  Predicted risk = 1 / (1 + exp(−Z))
```

The abbreviated spline terms above are cubic polynomial adjustments used to model non-linear relationships for that lab/vital across its range. The exact, fully expanded coefficients used by this calculator are in the app's source code (available on request) so the displayed equation and the computed result always match exactly.

How the equation becomes a percent risk

Each factor above contributes a weighted amount (its coefficient) to a running total, **Z**. Positive weights increase risk; negative weights decrease it. Z can be any positive or negative number and is not itself a probability.

Z is converted to a probability between 0% and 100% using the logistic function: **Predicted risk = 1 / (1 + e^{-Z})**. This is the standard conversion used by all logistic regression models -- it compresses the weighted sum into a valid probability while preserving its ranking (higher Z always means higher predicted risk).

Reference / supporting publication: Predicting venous thromboembolism among hospitalized adults: a protocol for development and validation of an implementable real-time prognostic model. *Diagnostic and Prognostic Research*, 2025.
This is the published study protocol; the final results manuscript is in progress and this link will be updated once it is available.

Risk categories

Predicted risk	Category
< 1%	Low
≥ 1% to < 2%	Elevated
≥ 2%	Critically High

Cutoffs are provisional (placeholder values requested for initial release) and should be revisited once calibration/decision-curve analysis defines them formally.

Shiny Application Developed by:

Hank Domenico, Ben French, Ryan Moore, Dan Byrne, Ben Tillman, Amanda Mixon

Disclaimer:

This calculator has been developed for use in research and has been retrospectively evaluated at Vanderbilt University Medical Center; thus it should not be used for general clinical practice at this time. This model is intended to be used as an evidence-based tool and does not replace a clinician's clinical judgment.

For Nurses:

Version 1: The risk score will be embedded in the vascular perfusion flowsheet within EPIC.

Version 2: The risk score will display as an alert on "the brain", which is a centralized portion of EPIC for patient data visualization and documentation.

Due to the nature of this adaptive trial, versions may be further adapted based on interim analyses.

Day 1:
Patient gets admitted to inpatient care. Patient is randomized to intervention or control. If randomized to the intervention arm, the clinical team will see the risk score which will be displayed for review upon admission. The clinical team will review the risk score in conjunction with other clinical factors to decide whether the patient needs prophylaxis and order what they deem appropriate or determine if there is a contraindication to prophylaxis, if applicable.

Day 2:
The model will update every 24hours. Clinicians will be notified of the updated risk score to review the patient's risk in real-time and change prophylaxis accordingly if the risk score has significantly increased. This process will repeat until 1) patient receives and accepts prophylaxis; 2) clinician notes contraindication; or, 3) patient is discharged from the hospital or dies while hospitalized.

6.0 Risks

This protocol presents no more than minimal risk to patients and healthcare clinicians. All patients admitted to the inpatient setting at Vanderbilt Adult Hospital are assessed for VTE risk on admission as part of standard care. However, current protocols are not standardized across services. This model aims to further inform clinicians of patients' risk by presenting a risk score alongside pertinent information (i.e. factors contributing to risk score and how the risk score compares to average risk). This risk score will update daily based on most recent labs, vitals, etc and will provide additional information to clinicians when making decisions about prophylaxis. Clinicians will continue to use standard of care procedures when assessing risk, with the addition of the information (risk score) provided by the model. There is clinical equipoise as to whether providing a data-driven, patient-specific risk score will change ordering behavior for providers versus not providing a risk score.

Adverse events include potential increased bleeding risk if prophylaxis is ordered based on the model output that may have otherwise not been ordered.

The model is not intended to dictate care of the patient, and the clinical team may ignore the risk score and proceed with prophylaxis as they see fit.

There are risks associated with standard clinical care, including:

- Risk of bleeding inherent to VTE prophylaxis
- Discomfort with administration of prophylaxis (adherence to treatment)

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The MPIs are responsible for monitoring study data, assuring protocol compliance, and conducting safety reviews. Adverse events or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately to the MPI and responsible IRBs, and in writing within 7 days to the IRB and any appropriate funding and regulatory agencies. The MPI will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings. Annual reports will be submitted to the responsible IRBs summarizing study progress, adverse events, complaints about the research or withdrawals, and any protocol violations.

We will follow the VHRPP guidelines that require investigators to promptly notify the IRB within 7 days of the occurrence when unexpected AEs occur. These are events that could possibly be related to the intervention, or occur more frequently or are more severe than anticipated. VHRPP requires that any AE that is unexpected and related or possibly related to the research be reported. Risks that are described in the protocol do not have to be reported as Study Adverse Events (SAEs), unless the expected SAE occurs more frequently or is more serious than expected. One exception to this rule is in the case of a death. All deaths must be reported, whether or not the death was related to the research.

AEs or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately, within twenty-four (24) hours of their discovery to the PI, and in writing within 7 (seven) days to the IRB and any appropriate funding and regulatory agencies. The PI will apprise fellow investigators and study personnel of all AEs that occur during the conduct of this research project through regular study meetings. Annual reports will be submitted by the study coordinator to the responsible IRBs summarizing study progress, AEs, complaints about the research, and any protocol violations.

To ensure the safety of participants, we have identified a Data Safety Monitoring Board (DSMB) which will meet biannually for the duration of the trial. The DSMB is comprised of one external biostatistician, one external hematologist as a subject matter expert, and one internal general internist leading a similar ongoing trial. The DSMB will review blinded data for baseline characteristics, process measures and study outcomes, by group assignment, with the primary purpose of identifying evidence of inappropriate risk to patients. Unblinded data will be available upon request if the DSMB deems it necessary to adequately assess patient safety. We will report on interim analyses and provide data on safety outcomes for the DSMB to review.

8.0 Study Withdrawal/Discontinuation

List the process for withdrawing from the study. List the process for being withdrawn from the study and the indications for withdrawal.

Since there is no active recruitment for this study, there will be no active withdrawal. Participation in the trial will end in the case a patient dies during hospitalization or is converted to hospice care at Vanderbilt Adult Hospital. Patient data up to the point of withdrawal will be retained and analyzed. Additionally, clinicians may choose not to act on the model's recommendations at any time. Retention in the study will last for the hospitalization period, which will be variable in length by patient.

9.0 Statistical Considerations

For interim analyses, we will use a quality outcome: model-indicated prescription of HA-VTE prophylaxis (i.e., implementation among high-risk patients but not among low-risk patients). A readily defined, proximal binary outcome will facilitate timely within-trial adaptations. Use of an intermediate outcome is appropriate given the strong association between the intermediate outcome (e.g., HA-VTE prophylaxis) and the primary outcome (e.g., HA-VTE). At each interim analysis, we will calculate an odds ratio comparing the odds of model-indicated prescription of HA-VTE prophylaxis between the intervention and control groups. If the posterior probability that the odds ratio is greater than a minimum clinically relevant difference (e.g., >1.05) is high (e.g., >95%), we will accept the current implementation of the intervention as effective and adopt it for the duration of the trial. If the posterior probability that the odds ratio is greater than a minimum clinically relevant difference (e.g., >1.05) is small (e.g., <20%), we will abandon the current implementation of the intervention due to futility and subsequently adopt a new implementation of the intervention. We anticipate that interim analyses will occur every 3 months, subject to sufficient enrollment to support interim analyses.

The final analysis will compare the odds of HA-VTE between the final implementation of the intervention and the common control group of patients. Patients will be analyzed according to the group to which they were randomized regardless of whether HA-VTE prophylaxis was ordered (i.e., intent to treat). We will calculate the Bayesian posterior probability that the odds ratio is <1.

Among all adults admitted to VUMC during the past 3 years, the rate of HA-VTE was 9.4 per 1000 (A.2.1). We expect at least 65,000 adults will be enrolled during the 1.5-year study period. Consider equal allocation of all eligible patients to either an intervention or control group. A two-sample binomial test achieves at least 80% power to detect an absolute difference of at least 2.0 per 1000 in the rate of HA-VTE between the intervention and control groups (7.4 versus 9.4 per 1000, respectively) with a type-I error rate of 5%. A risk difference of 2.0 per 1000 translates to 65 HA-VTEs prevented among the intervention group. The protocol will be supplemented with the results of ongoing simulation studies demonstrating the Bayesian operating characteristics of the trial.

10.0 Privacy/Confidentiality Issues

All efforts will be made to keep personal information and research records private throughout this study. Records and documents pertaining to the conduct of this study will be kept in HIPAA compliant, secure, password protected databases on servers secured in the VUMC/VUH data center. All patient data will be coded using a unique study ID. No PHI will be shared outside of the key study personnel. Records will be maintained in accordance with IRB, institutional, and sponsor policies. Results from the study will be published using aggregate results, but no individual subjects will be identified in the publication. No data will be submitted to the FDA.

11.0 Follow-up and Record Retention

The anticipated duration of the study is 18 months commencing August 1, 2026 and concluding February 1, 2028. As this study does not include direct contact with enrolled participants, there will be no follow-up. Data collected from the study will be retained for data collection for 7 years following conclusion of the study. After 7 years, raw data will be destroyed. A de-identified copy of the data will be kept for our records. All data will be stored securely at Vanderbilt after study conclusion.