Research Protocol:

Clinical Predictors for Venous Thromboembolism in Patients with a History of Thrombosis

Short Title: PREDICTORS Study

Protocol Number: 20140622-01H

Funding Source: Heart and Stroke Foundation of Canada

Principal Investigator: Dr. Gregoire Le Gal

Coordinating Centre: Ottawa Hospital Research Institute

Study Personnel: Dr. Marc Rodger, Dr. Phil Wells, Dr. David Anderson, Dr. Susan Kahn, Dr. Michael Kovacs, Dr. Timothy Ramsay

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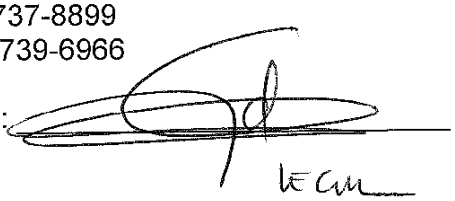
Signature:  Date: Jan 7, 2015

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Confidentiality Agreement

This protocol contains confidential information belonging to Dr. Gregoire Le Gal except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Dr. Gregoire Le Gal and The Ottawa Hospital should be promptly notified.

Signature:_____Date:_____

List of Abbreviations

BMI	Body Mass Index
CDR	Clinical Decision Rule
CIAC	Central Independent Adjudication Committee
CRF	Case report Form
CUS	Compression Unltrasound
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
OHRI	Ottawa Hospital Research Institute
PE	Pulmonary Embolism
VTE	Venous Thromboembolism
V/Q	Ventilation-perfusion

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PROTOCOL SUMMARY

Protocol Title	Clinical Predictors for Venous Thromboembolism in Patients with a History of Thrombosis
Protocol Number	20140622-01H
Coordinating Centre	Ottawa Hospital Research Institute
Protocol Date	Version 2, 06-Nov-2014
Population	Outpatients presenting with suspected acute recurrent VTE.
Objectives	Primary Objective: To assess the accuracy and usefulness of the Wells DVT, Wells PE and Geneva clinical decision rules in patients with a clinically suspected recurrent VTE. Secondary Objectives: • To assess the utility of recalibrating the existing clinical decision rules. • To derive a new CDR, specific to patients with a suspected recurrent VTE, and to assess whether this CDR would improve risk stratification as compared with existing CDRs. • To assess the accuracy of D-dimer testing in patients with suspected recurrent VTE both on and off anticoagulation. • To evaluate the accuracy of current CDRs in patients on anticoagulant therapy at the time of suspected recurrent VTE.
Duration	All consecutive eligible patients will be approached for enrolment into this study over 3 years.
Design	This is a multicentre, observational cohort study to prospectively identify potential predictors of recurrent VTE. The predictive value of individual and combined candidate predictors will be evaluated in patients with suspected recurrent VTE. All suspected recurrences will be blindly and independently adjudicated.
Significance	If the newly developed clinical decision rule is proven to accurately determine the pre-test probability in patients with a suspected acute recurrent VTE, it could be integrated in diagnostic strategies that might lower cost, avoid radiation exposure and potentially decrease over-diagnosis of patients with suspected recurrent VTE.

Target Sample Size

A total of 745 participants will be enrolled at Canadian sites.

Participant Population

Inclusion Criteria

1. Outpatient with clinically suspected acute recurrent DVT or PE regardless of whether the previous event was a DVT or PE
2. Age ≥18 years old
3. Willing and able to give informed consent

Exclusion Criteria

1. Life expectancy less than 3 months
2. Suspicion of upper extremity thrombosis or thrombosis at an unusual site (e.g. cerebral or abdominal venous thrombosis)
3. Previous VTE was distal DVT or subsegmental PE
4. Suspected recurrent VTE is asymptomatic
5. Previously enrolled in this study

2. BACKGROUND AND RATIONALE

2.1 Background Information

The diagnostic management of suspected recurrent venous thromboembolism is challenging, since missing the diagnosis exposes the patient to the risk of (potentially) fatal PE while a false-positive diagnosis leads to unnecessary lifelong anticoagulant treatment and exposes patients to (potentially) fatal bleeding. Furthermore, not treating or a delay in treatment of recurrent DVT could worsen the symptoms of the post-thrombotic syndrome (PTS) [17;18].

A suspected acute recurrent VTE is common: among all patients with a suspected VTE, 20% have a history of previous VTE. In the 18 months after the withdrawal of anticoagulant therapy, 40% of patients will present with suspected recurrent VTE. The mainstays of VTE diagnosis include clinical probability, diagnostic imaging, and D-dimer testing. However, there are important implications for diagnostic management when a patient has a history of prior thrombosis. Few research studies have focused specifically on patients with suspected recurrent VTE and no study has focused on the clinical predictors of VTE in patients with suspected VTE and a history of VTE.

Clinical probability assessment is a crucial step in the management of patients with clinically suspected VTE. Pretest probability refers to the probability of a target disease or disorder being present before a diagnostic test result is known. Current diagnostic strategies for VTE rely on the sequential use of diagnostic tests based on the pretest probability of disease. Clinical decision rules (CDR) estimate the probability of a clinical outcome using simple available clinical data. Several predictive factors and CDR have been established to estimate the pretest probability of VTE.[1-5] The most commonly used CDR for suspected DVT is the Wells rule, and for suspected PE the Wells and Geneva rules. The pretest probability can aid in the interpretation of imaging test results, and to identify a group of patients at low risk of disease in whom a less intensive diagnostic work up is warranted. For example, VTE can be safely excluded in a patient deemed to be at low risk according to the CDR in combination with a negative D-dimer test result.[6;7]

Diagnostic Imaging

Post-hoc analyses of diagnostic studies have been reassuring in terms of the safety of ruling out VTE on the basis of a non-high pretest probability using the Wells or Geneva rule in combination with a negative D-dimer in patients with a previous history of VTE.[4;9] However, the proportion of patients in whom the diagnosis could be ruled out non-invasively was very low: approximately 10%, as compared with 30% among all-comers with suspected VTE.[10]

Moreover, residual thrombosis is often present after a VTE event (up to 50% of patients at one year). Therefore, it is more likely to misdiagnose a recurrent VTE in saying it is present, while it's absent. As a result of over diagnosis, these patients have a long period of exposure to anticoagulants and the associated risk of major bleeding.

Patients with a high risk according to the CDR and/or a positive D-dimer test result require imaging. However, diagnostic imaging of a suspected recurrent VTE is more challenging to interpret if a residual thrombus is present, and distinguishing a recurrent acute thrombosis from a residual thrombosis is often difficult on imaging. In a study in which all patients with a first unprovoked VTE underwent baseline imaging before discontinuing anticoagulant therapy, almost one half of patients had a suspected VTE during the first 18 months of follow-up. In 20% of patients with suspected recurrent VTE, the imaging test was positive for VTE but unchanged as compared with baseline, which means that without the results of baseline imaging tests, up to 20% of patients could have received a false-positive diagnosis of recurrent VTE.[11] In another study by Tan et al., 32% of patients with a suspected acute ipsilateral recurrent DVT had an inconclusive ultrasound result, yet all patients were treated with anticoagulants.[13] In patients with no baseline imaging available, [12;13] this may result in misdiagnoses in patients with previous VTE, with consequent unnecessary anticoagulant therapy conveying a risk of major bleeding in those over-diagnosed or potentially fatal recurrent PE in untreated patients with a true recurrence. Therefore improved risk stratification of suspected recurrent events before imaging could be of high clinical value to increase the yield of CDR and D-dimer, and thus decrease the need for imaging in this subgroup of patients. Potential benefits include reduction in radiation exposure, misdiagnosis, and costs associated with imaging, drug treatment, monitoring and medical follow-up.

2.2. Available Knowledge of Risk Stratification before Imaging

What follow are a review of the literature on predictors of recurrent VTE and the results of a retrospective study that we've performed to look at the predictive value of individual potential clinical predictors.

Clinical Probability Assessment
The Wells rule is the most well validated CDR for DVT (Refer to **Appendix A**: *Current Clinical Decision Rule for Suspected DVT*). In the 'original' Wells rule the item of 'deep vein thrombosis in the past' was not included[21] but this item was added to a subsequent version of the rule, adding one point to the rule if it is present.[7] Hence, by design, the Wells rule will have a lower specificity (less likely to be low pre-test) in patients with prior VTE. Furthermore, because the symptoms: increase in calf diameter, swelling of the leg and pain on the deep vein tract, are also symptoms of PTS and are often present in patients with a history of DVT, the performance of these variables in patients with a suspected recurrent DVT might be altered.

In patients with clinically suspected recurrent PE, the challenges for accurate diagnosis are similar to patients with suspected recurrent DVT. Patients often have persistent complaints of dyspnea after a PE.[22] In patients with suspected PE the Wells rule and Geneva rule are the most validated rules (Refer to **Appendix B**: *Current Clinical Decision Rules for Suspected PE*).[2-5] Both rules include an item related to a history of VTE in the past. Similarly to DVT, patients with a previous VTE are less likely to be classified as having a low clinical probability of PE: 26%, versus 58% in patients with no previous VTE in a post-hoc analysis of a PE diagnostic study using the Geneva score.[4] Of note, existing CDR use 'previous VTE'

as a single criterion, regardless of the location, characteristics and time elapsed since the previous episode, although these criteria could have an important impact on the pretest probability.

D-dimer Testing
In patients with a suspected VTE event, D-dimer testing, in combination with a CDR, can safely rule out a VTE.[7;23] In a study in 300 patients with clinically suspected recurrent DVT by Rathbun et al., 45% of the 300 patients had a negative D-dimer test and these patients were not treated with anticoagulants on the basis of this test alone.[20] One patient who had recurrent DVT excluded by a negative D-dimer test had confirmed VTE during 3 months follow-up (0.75% (95% CI, 0.02-4.09%). The Wells score in combination with a D-dimer test has been used to manage patients with clinically suspected acute recurrent DVT in a study by Anderson et al.[19] In this study, 16 of 105 patients (15%) had an unlikely clinical probability and a normal D-dimer test; during three months follow-up none of these patients had a recurrent DVT. This study suggests that an unlikely clinical probability in combination with a normal D-dimer test result could potentially be used to exclude a DVT, but this strategy should be evaluated in a larger cohort of patients. The proportion of confirmed recurrent DVT was 22%. In a third study, among 308 patients with suspected acute PE with a VTE in the past, the D-dimer test was negative in 49 patients (16%), and none of them had a recurrent VTE during the 3-month follow-up: failure rate 0% (95% CI, 0.0-7.9%). The proportion of confirmed recurrent PE was 40%.[4]

In conclusion, D-dimer testing may play a role in excluding a recurrent VTE; however the presently available studies show broad confidence intervals for the 3 month recurrent VTE failure rates after a negative test result. Most importantly, the combination of current CDRs and D-dimer testing shows a low proportion (10-16%) of patients who could have VTE excluded by a low pretest probability and a negative D-dimer test result.

2.2.2. A survey of thrombosis experts

As a second approach to identify candidate predictors, we performed a survey in our own nation-wide collaborative research group to evaluate what the thrombosis experts consider potential predictors of recurrent VTE, based on their clinical experience in managing these patients. The following items were proposed by thrombosis experts as potential clinical predictors and will be collected in this study:

Pulmonary embolism
- Leg symptoms and signs of DVT
- Tachycardia
- Cancer
- Recent surgery or immobilization
- Subtherapeutic INR or recent dose reduction
- Clean X-ray
- No alternative diagnosis

Deep vein thrombosis of the leg
- Tenderness in deep vein distribution

- New onset of significant leg swelling
- New onset of edema or worsening of chronic state of lower extremity edema
- Cancer
- Subtherapeutic INR or recent dose reduction
- Recent surgical procedure
- No alternative diagnosis

General predictors for DVT and PE

- Age
- Gender
- Whether previous event was provoked/unprovoked
- Active cancer
- D-dimer testing at moment of suspected recurrence and on baseline visit
- Recent (within one year) discontinuation of anticoagulation after previous event
- Estrogen therapy

2.2.3 Retrospective cohort study in patients with suspected recurrent VTE

Finally, we examined potential predictors of recurrence by performing a post-hoc analysis of the REVERSE I study[26]). Each patient in the REVERSE I cohort that had a suspected recurrent VTE during follow-up were screened for eligibility in the post-hoc analysis. Only patients with a first adjudicated suspected recurrent event were included. Potential clinical predictors of recurrent VTE consisted of clinical predictors collected at the baseline visit, information collected in physicians' clinical notes, and laboratory or imaging results at the time of the suspected recurrent VTE. The predictive value of each predictor was determined by the Chi-square test for nominal data and the unpaired 2-tailed T-test for continuous data.

In the REVERSE I cohort, out of the 646 patients who were followed, 402 patients had a suspected recurrent VTE within a mean of 20.2 months (range: 0 – 97 months) of follow-up. Of these, 376 patients were eligible for our study: 52.7% of patients were males, and the mean age was 53.1 years (± 17.5). Among all suspected recurrent VTE events, male gender and a positive D-dimer result at the time of suspected recurrent VTE ($p < 0.01$), as well as symptoms occurring for 10 days or less at the time of presentation ($p < 0.05$) were in favor of a recurrent VTE diagnosis. In addition, mean age was higher in patients with a confirmed recurrent VTE ($p < 0.05$). Patients who had a previous DVT confirmed were at higher risk of having a recurrence confirmed at their next suspected event than when the previous event was a proven PE ($p<0.05$).

This is the first study to show that predictors for the diagnosis of a recurrent VTE may be different than predictors for the diagnosis of a first VTE. For instance, our results show that male gender is not only a risk factor for recurrent VTE[27], but is also an important predictor for confirmed VTE among patients with suspected recurrent VTE. None of the existing CDRs take gender into consideration. The main limitation of this analysis is that clinical information at the time of the suspected recurrence was extracted from patients' charts, and therefore is subject to bias, as the amount of clinical data in the case report form was limited. Nevertheless, the findings of this post-hoc analysis, along with the survey and literature review, support the need for a modified CDR specific to patients with a history of VTE. Improved diagnostic

management in this population would lead to more optimal clinical management and improved safety for these patients.

1. STUDY OBJECTIVES

1.1 Primary Objective

To assess the accuracy and usefulness of the Wells DVT, Wells PE and Geneva clinical decision rules (CDR) in patients with a clinically suspected recurrent Venous Thromboembolism (VTE).

1.2 Secondary Objectives

- To assess the utility of recalibrating the existing clinical decision rules.
- To derive a new CDR, specific to patients with a suspected recurrent VTE, and to assess whether this CDR would improve risk stratification as compared with existing CDRs.
- To assess the accuracy of D-dimer testing in patients with suspected recurrent VTE both on and off anticoagulation.
- To evaluate the accuracy of current CDRs in patients on anticoagulant therapy at the time of suspected recurrent VTE.

3. STUDY DESIGN

This is a multicentre, observational cohort study to prospectively identify potential predictors of recurrent VTE. The cohort consists of outpatients in the Thrombosis Clinic that are evaluated for suspected recurrent DVT and/or PE. Diagnostic management of suspected recurrent VTE will be according to usual clinical practice; therefore all patients with suspected recurrent VTE will receive a diagnostic work–up as per local standards of care. All consecutive eligible patients will be approached for enrolment into this study. A total of 745 participants will be enrolled at Canadian sites.

3.1 Patient Safety

This observational study poses minimal risk to participants. The study procedure consists of some additional questions and one follow-up call if the diagnosis is excluded. The risks associated with venipuncture (discomfort or bruising) are disclosed in the consent form. As per usual clinical care, all patients will be instructed on signs and symptoms of DVT and PE and advised to return to the hospital in case of any suspicion of a DVT or PE. As this is an observational study, adverse events will not be collected.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

This study will be conducted at Canadian sites. Consecutive outpatients presenting to the Thrombosis Clinics of the participating hospitals with signs or symptoms suggestive of recurrent VTE will be screened for eligibility.

4.1 Eligibility

Eligibility status of all participants must be confirmed by the local investigator or designate before enrolment. It is important that no exceptions be made to the eligibility criteria. Questions related to the eligibility requirements or specific criteria must be discussed with the coordinating centre before enrolment.

4.2 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study.

1) Outpatient with clinically suspected acute recurrent DVT or PE regardless of whether the previous event was a DVT or PE
2) Age ≥18 years old
3) Willing and able to give informed consent

4.3 Exclusion Criteria

Participants who meet one or more of the exclusion criteria at baseline screening will be excluded from study participation.

1) Life expectancy less than 3 months
2) Suspicion of upper extremity thrombosis or thrombosis at an unusual site (e.g. cerebral or abdominal venous thrombosis)
3) Previous VTE was distal DVT or subsegmental PE or at an unusual site
4) Suspected recurrent VTE is asymptomatic
5) Previously enrolled in this study

4.3.1 Rationale for Exclusion Criteria

1) precludes complete follow-up; 2) and 3) there are uncertainties surrounding the characteristics, diagnostic management, treatment and prognosis of these entities. Inter-observer agreement in imaging interpretation is lower, the risk of recurrent VTE appears to be much lower, and patients' management remains very heterogeneous; 4) uncertainties surrounding the clinical relevance of these findings; 5) prevents duplication of study data.

6. STUDY PROCEDURES

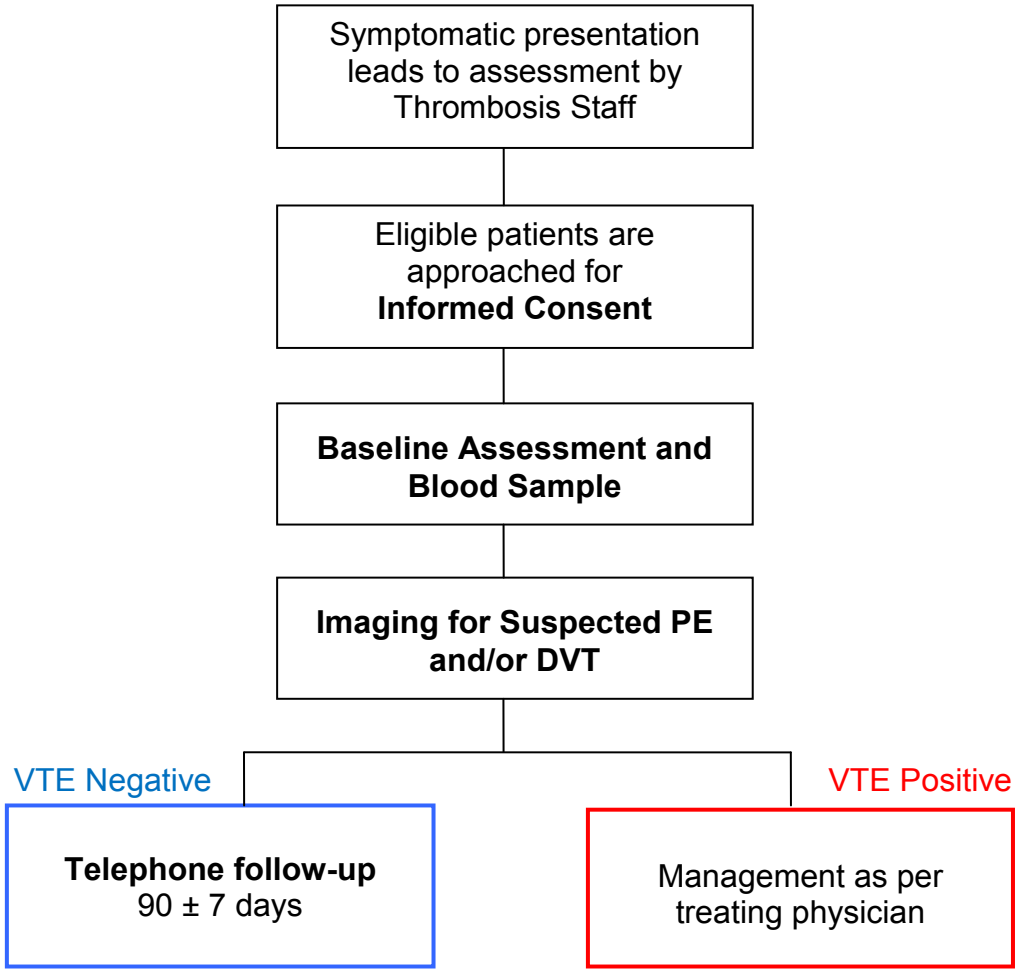

Figure 1: Study Flow

6.1 Screening and Consenting

Potentially eligible patients will be identified by a healthcare professional according to institutional policy on privacy. The investigator or delegate will obtain written informed consent from the patient before collecting any data or performing any study-related procedures.

Patients who meet the inclusion criterion, but who are excluded due to an exclusion criterion or who do not provide written consent will be recorded on a screening log.

6.2 Baseline Assessments and Diagnostic Management

6.2.1 Clinical examination and data collection

Once a patient has consented to participate, an investigator or attending physician will complete an assessment of suspected clinical predictors of recurrent VTE and will calculate the participant's clinical pretest probability using the existing CDRs. The diagnostic work-up of each participant will be handled in line with the current standard of care at the discretion of the treating physician. (For reference of the current standard practices, refer to ***Appendix C:*** Flow Chart of Suggested Diagnostic Approach for Assessing Suspected Recurrent VTEs)

Data collection of clinical predictors will be completed by the investigator or delegate, by way of participant interview, reviewing medical records, and physical examination. (For a complete list of clinical predictors, refer to ***Appendix D****: Collection of Clinical Predictors for Suspected Recurrent VTE*). Clinical notes and results of all diagnostic tests for suspicion of VTE, as well as the diagnostic conclusion and therapeutic management will be recorded for all patients.

6.2.2 D-dimer testing

All study patients will have a blood sample drawn at the time of suspected recurrence and frozen for central D-dimer testing. Serum samples will also be stored for future potential predictor assessment (other D-dimer assays or other biomarkers). Samples will be shipped in batches to the coordinating site and D-dimer levels will be determined in all patients using a single commercial assay (VIDAS D-dimer Exclusion II, bioMérieux Inc, Durham, NC). Please refer to the resource manual for details on processing, storage and shipping of D-dimer samples.

6.2.3 Imaging

All imaging results will be recorded and kept in the patient's study folder. Confirmed recurrent VTE will be treated according to the standard of care at the local institution by the primary physician.

Suspected DVT
Current practice for patients with suspected recurrent DVT is to receive a compression ultrasound (CUS) of the symptomatic leg to confirm or exclude the diagnosis. CUS will assess venous compressibility of the proximal veins from the common femoral vein down to and including the calf vein trifurcation.

Suspected PE
Suspected recurrent PE is most commonly investigated by CT pulmonary angiogram (CTPA) and confirmed by an intraluminal filling defect in a subsegmental or greater pulmonary artery. Alternatively, a ventilation-perfusion (V/Q) lung scan will assess for a "high probability" perfusion defect.

6.3 Follow-up Visits

All patients in whom a recurrent VTE is ruled out will receive a follow-up call at 3 months (90 ± 7 days) after the initial evaluation using a structured interview script. Research coordinators will be trained by the investigator or multicenter coordinator prior to follow-up to ensure consistency in eliciting new signs and symptoms of DVT and PE between sites. Any new leg or chest symptoms reported to study personnel during study follow-up will prompt clinical and diagnostic assessment. Participants with suspected VTE will be assessed in the Thrombosis Clinic (or Emergency Department) and ordered diagnostic testing as judged necessary by their physician or the investigator. If participants report that they sought medical attention for complaints of possible VTE, medical records and imaging results will be collected to prepare an adjudication report. Any participant who seeks medical attention during their follow-up period and is once again not diagnosed with a recurrent VTE will have an additional call at 90 (± 7 days) days after they were last assessed.

All deaths during follow-up will prompt chart review and all available information including interviews with next of kin will be documented to permit preparation of an adjudication report to determine if the death is PE related.

The follow-up period is relatively short and therefore participant loss to follow-up should be minimal. However, for participants that cannot be reached by phone, an exhaustive search will determine if outcome events have occurred (including calls to next of kin or pre-identified contacts, obituary searches, retrieval of death certificates, review local hospital databases) prior to participants being declared lost to follow-up.

9. STATISTICAL CONSIDERATIONS

9.2 Sample Size Calculation

Beyond our primary objective of validating existing CDRs, we aim at enrolling enough participants to allow the derivation of a new CDR specific to patients with suspected recurrent VTE, in order to assess whether such a new CDR could improve risk stratification in this patient population. As per accepted methodological criteria for the development of CDRs, 5-10 patients per predictor studied are required in the smallest outcome category.[29] At this point, we don't know if we will be able to derive a single CDR for recurrent VTE or if deriving two separate CDRs for DVT and PE will be more useful. Our sample size estimation takes this uncertainty into account. We would like to be able to use up to 10 predictors for patients with suspected DVT with a history of VTE and separately up to 10 predictors for patients with suspected PE with a history of VTE; this means that the required study sample is 100 participants with a confirmed recurrent DVT and 100 participants with confirmed recurrent PE.

In a study by Le Gal et al. for the diagnostic management of recurrent VTE, 26.6% of participants with suspected VTE had the diagnosis confirmed.[11] In another paper 40.3% of the participants with suspected PE with a history of VTE had their diagnosis confirmed.4 In the retrospective study that we performed as preparation for this prospective study, 29% of the participants with a suspected recurrent DVT had their recurrence confirmed and 25% of the participants with a suspected recurrent PE had the diagnosis confirmed.

For DVT, in order to be conservative, we used the percentage from our retrospective study, that is, 29%. That means that we need to enroll 345 participants with suspected recurrent DVT to have 100 participants with a confirmed recurrent DVT. For PE, using an estimate of a 25% confirmation rate we need 400 participants with a suspected recurrence to have 100 participants with confirmed PE. Total sample size for the study is estimated at 745.

If we consider that 15% of the potentially eligible participants approached for this study will be found to be ineligible or will not consent for this study, we need to screen 397 patients with a suspected recurrent DVT and 460 patients with a suspected recurrent PE for this study. Hence, to meet our total sample size of 745 we will need to screen approximately 857 for eligibility.

9.5 Primary Outcome Analysis

The primary analysis is the validation of existing CDRs. The Wells DVT score will be computed in all participants with suspected DVT, and both the Wells' PE score and revised Geneva score will be computed in participants with suspected PE. Calibration will be assessed by comparing predicted and observed rates of confirmed VTE (Hosmer-Lemeshow 'goodness-of-fit test'), and discrimination will be assessed using the area under the receiver operating characteristics curve (c-statistic). Further, the proportion of participants with the combination of a non-high clinical probability and negative D-dimer test, and the false-negative rate of this combination (ie the proportion of participants with confirmed recurrent VTE among those with a non-high clinical probability and negative D-dimer) will be estimated along with their 95% confidence intervals.

9.6 Secondary Outcome Analysis

9.5.1 Recalibration / minor adjustment to existing rules

Recalibration

For each existing CDR, a multivariate regression analysis including all predictors from the CDR will be conducted. The regression coefficients obtained from this model in our sample will be examined to evaluate whether changes in the points given to each predictor in the rule need to be modified in patients with a suspected recurrent VTE.

Minor adjustments

For each existing CDR, a multivariate regression analysis including all predictors from the CDR will be performed. Candidate predictors will also be included in the analysis, but keeping in the model predictors from the CDR. Should one or two candidate predictors significantly improve risk stratification, a modified score could be proposed for patients with suspected recurrent VTE. Potential improvements in classification will be assessed using the Net Reclassification Improvement and the Integrated Discrimination Improvement indices.

9.5.2 Derivation of a new CDR

Univariate Analysis

Univariate analysis will be used to assess the association between each variable and VTE recurrence. This process will aid selection of the best variables for the multivariate analysis. The appropriate univariate technique will be chosen according to the type of data.

Multivariate Analysis

Multivariate analysis will derive one model to predict recurrent VTE. Those variables found to be strongly associated with the outcome measure ($P<0.05$), by the univariate analysis and have good inter-observer reliability (kappa >0.6), will be combined using logistic regression. For continuous and ordinal variables various cut-points will be examined to determine the optimal cut-point(s). The derived CDR must be easy to use by clinicians and therefore should contain as few variables as possible. Thus, only the most informative variables will be kept in the final model. Points for the score will be attributed according to regression coefficients. The CDR will be presented in clear narrative form that does not require computation or use of statistical aids. Discrimination and calibration of the new CDR will be estimated and compared to those obtained with existed/modified CDRs using the same indices as described above.

9.5.3 D-dimer testing

We will estimate what the proportion of participants will be with a non-high pre-test probability (using all the possible stratification tools described above) and negative D-dimer test result and in whom imaging could potentially be withheld. We furthermore will estimate what the false negative rate will be in this proportion of participants. These proportions will be computed along with their 95% confidence intervals.

9.5.4 Participants treated with anticoagulant therapy

Evaluate the accuracy and usefulness of CDR and D-dimer testing in participants with a suspected recurrent VTE who are receiving therapeutic anticoagulant therapy.

9.5.5 Compare indeterminate imaging results in participants with and without available information about previous imaging

We will compare the proportion of participants with indeterminate results in participants with and without available baseline imaging. We will assess how these participants were managed (treated vs. not treated). Of the participants who were not treated we will evaluate the 3 months VTE failure rate.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data collection is the responsibility of the designated research study staff at the clinical centre under the supervision of the local Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study. Study Case Report Forms (CRFs) are designed to record the disease status,

treatment, observations, follow-up and other pertinent data on each enrolled study participant. Participants will be identified by a unique study ID number. Data reported on the CRF derived from source documents must be consistent with the source documents. All source documents and laboratory reports must be reviewed by the designated research study staff at the participating clinical centre.

10.2 Data Management

Data management will be performed using a web-based system designed by the OHRI Data Management Services. Only trained research personnel from each site will have authorization with an access password to enter and modify electronic case report forms (eCRFs). The web based system functions with a secure server and backups will be done regularly. A user tracking system will track the date and time that users enter or modify data. Once eCRFs are completed, data verification may result in additional requests to clarify the data.

10.3 Retention of Study Records

To enable future evaluations and audits, the local investigator must maintain confidential study documentation and ensure the retention of the study documents for a minimum of 10 years, as per OHRI, the sponsor. Study documents will include the identity of all study participants (sufficient information to link records, e.g., eCRFs and hospital records); all original signed Informed Consent Forms, and source documents.

After a minimum of 10 years, all study documents will be destroyed (via incineration or shredding) at the local site.

10.4 Quality Assurance

Study related procedures must be conducted in compliance with the protocol, amendments, regulations and guidelines, in order to ensure data integrity. Any deviations from the protocol will be accurately documented, reported and reconciled.

Protocol deviations refer to incidents involving non-compliance with the protocol that are unlikely to have a significant impact on the on data integrity.

If a protocol deviation occurs the following procedures will be followed:

- The local investigator or delegate will document and explain any deviation from the approved protocol
- Deviations from the protocol must be reported in the study source document
- Deviations will be reviewed during monitoring visits.
- A log of all deviations at the site must be maintained (ideally in an excel spreadsheet)

As this is an observational study that does not affect patient safety, there will be no protocol violations to collect.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Research Ethics Board

This study will be reviewed and approved by the Ottawa Health Science Network Research Ethics Board before commencement of the study. Each participating site must also obtain Ethics Board approval before study initiation. Annual ongoing review will also be performed. Any amendment to the protocol or informed consent form must be approved by the local Research Ethics Board before implementation.

11.2 Informed Consent Forms

Prior to inclusion in the study, the investigator, or his designee, will provide each participant (or the participant's acceptable representative), full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The participants must be informed about their right to withdraw from the study at any time. Written participant information will be given to each participant before enrolment. The investigator or his designee will obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all participants prior to inclusion in the study.

11.3 Participant Confidentiality

To protect the participant's confidentiality, source documents containing personal identifiers and informed consent forms will be kept separate from research notes and worksheets. Case report forms will not contain any identifying information. The identification log which links the identification of the participant to the assigned participant code will, according to local policy, be kept in a cabinet under lock and key or on a secure electronic drive.

12. STUDY ORGANIZATION

12.1 Study Coordination

The study will be coordinated through the Thrombosis Research Program, Ottawa Hospital Research Institute (OHRI), located at The Ottawa Hospital General Campus in Ottawa, Ontario. The multicentre coordinator, under the direction of the study Principal Investigator, Dr. Gregoire Le Gal, will be responsible for the overall study management including implementation of study protocol logistics, data management, and quality assurance related to study data. Local coordinators and site investigators will work together to screen, recruit, and follow study participants. Each co-investigator will be responsible for the conduct of the study at their respective sites.

12.2 Central Independent Adjudication Committee (CIAC)

All cases of confirmed VTE will be adjudicated by independent adjudicators. The results of all imaging tests performed at the time of suspected recurrent VTE will be compared with the patient's previous imaging, baseline or index, when available, and will be performed according to the predefined definitions (Refer to **Appendix E**:

Adjudication of Suspected Recurrent VTE Events). The adjudicators will confirm or refute suspected recurrent DVT and PE events.

The adjudication committee will also evaluate secondary outcomes including all suspected VTE events and deaths occurring during the 90 (±7) day follow-up period. The adjudication results will be the basis for the final analysis.

12.3 Steering Committee

A Steering Committee consisting of the study co-investigators will manage the overall conduct of the study and will meet regularly via teleconference or face to face meetings to monitor study progress, execution, management, analysis and reporting.

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15. APPENDICES

Appendix A: Current Clinical Decision Rule for Suspected DVT

Wells Rule for Suspected DVT

Clinical characteristics	Points
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	+ 1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+ 1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anaesthesia	+ 1
Localized tenderness along the distribution of the deep venous system	+ 1
Entire leg swollen	+ 1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	+ 1
Pitting edema confined to the symptomatic leg	+ 1
Collateral superficial veins (nonvaricose)	+1
Previously documented deep-vein thrombosis	+1
Alternative diagnosis at least as likely as deep-vein thrombosis	–2

Total score	Clinical probability	Prevalence of DVT
< 2 points	DVT unlikely	5.5 % (95%CI: 3.8 to 7.6%)
≥ 2 points	DVT likely	27.9 % (95%CI: 23.9 to 31.8%)

Appendix B: Current Clinical Decision Rules for Suspected PE

Wells Rule for Suspected PE

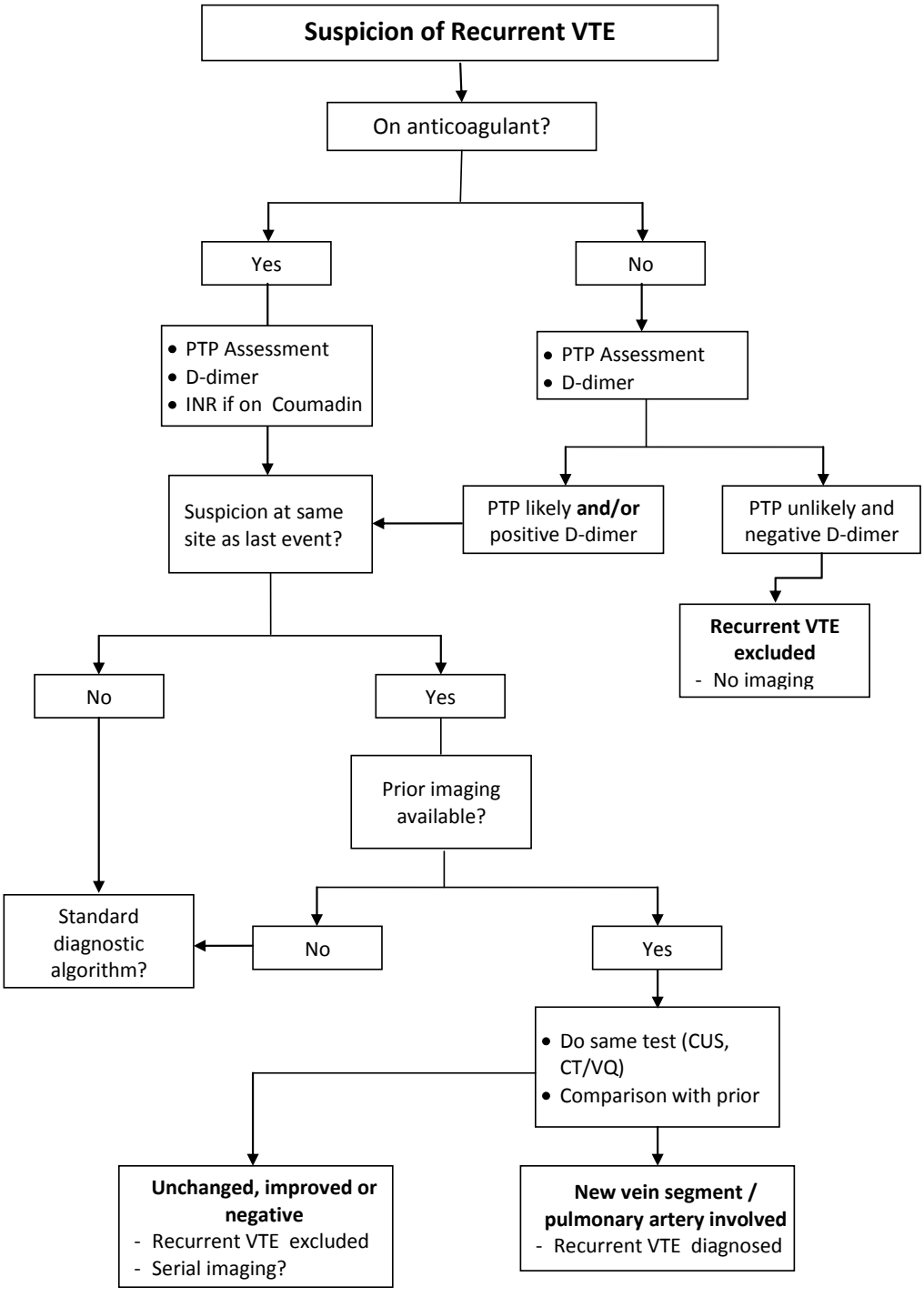
Wells score	
Active cancer	+ 1
Hemoptysis	+ 1
History of previous DVT or PE	+ 1,5
Heart rate > 100 /min	+ 1,5
Surgery or bedrest ≥ 3 days within 1 month	+ 1,5
Clinical signs or symptoms of DVT	+ 3
No alternative diagnosis as or more likely than PE	+ 3

Clinical Probability	Total Score	Prevalence of PE
Low	< 2	5.7 (3.7-8.2)
Intermediate	2-6	23.2 (18.3-28.4)
High	> 6	49.3 (42.6-56.0)
Unlikely	≤ 4	8.4 (6.4-10.6)
Likely	> 4	34.4 (29.4-39.7)

Revised Geneva score	
Age > 65 years	+ 1
Active cancer	+ 2
Hemoptysis	+ 2
History of previous DVT or PE	+ 3
Surgery or lower limb fracture within one month	+ 2
Unilateral edema and pain at palpation	+ 4
Spontaneously reported calf pain	+ 3
Heart rate	
75-94 / min	+ 3
≥ 95 / min	+ 5

Clinical Probability	Total Score	Prevalence of PE
Low	0-3	9.0 (7.6-10.6)
Intermediate	4-10	26.2 (24.4-28.0)
High	≥ 11	75.7 (69.0-81.8)

Appendix C: Flow Chart of Suggested Diagnostic Approach for Assessing Suspected Recurrent VTEs



Appendix D: Collection of Clinical Predictors for Suspected Recurrent VTE

Presenting history

Age
Gender
Duration of symptoms (days)
Inpatient/outpatient
Any dyspnea
Sudden dyspnea
Any chest pain
Pleuritic chest pain
Sudden chest pain
Hemoptysis
Affected leg: left/right
Leg pain
Cramps in the leg
Pruritus of the leg
Heaviness of the leg
Paraesthesia of the leg
Symptoms worse after walking and standing
Symptoms worse at end of the day
Symptoms best first thing in morning
Symptoms improve with rest or elevating leg
Symptoms worse after prolonged standing (>2 h, > 6 h)
Symptoms relieved after elevating leg
Symptoms relieved with compression stockings
Current use of anticoagulant therapy
Type and dose of anticoagulant therapy (e.g. LMWH, warfarin, NOACs)
Anxious personality

Risk factors

Family history of VTE (first and second degree)
Known thrombophilia
Pregnancy
Post-partum (<6 weeks after delivery)
Recent surgery (< 4 weeks, 8 weeks, 12 weeks)
Orthopedic surgery (< 4 weeks, 8 weeks, 12 weeks)
Active malignancy (< 6 months; malignancy required therapy, recurrent or metastatic, palliative)
Recent immobilization (< 10% walking hours for 3 consecutive days < 4 weeks, 8 weeks, 12 weeks)
Major trauma (< 4 weeks, 8 weeks, 12 weeks)
Congestive heart failure

Estrogen use
Paralysis of the leg
Paresis of the leg
Recent plaster cast (< 4 weeks, 8 weeks, 12 weeks)
Long distance flight (< 4 h, < 8 hours, < 12 hours, 12 hours and more), within 4 weeks, 8 weeks and 12 weeks

Characteristics of previous event and period between current and previous event
Number of previous events
Previous event: DVT/PE
Provoked/unprovoked
Time between previous event and current suspected recurrence
Location of previous event (in case of PE: central, lobar, segmental, subsegmental)
Location of previous event (in case of DVT: proximal, distal)
In case of DVT, affected leg (left/right)
Duration of anticoagulation
Type of anticoagulation (e.g. UFH, LMWH, warfarin, NOACs)
Previous use of compression stockings
Current use of compression stockings
Duration of use of compression stockings
Residual thrombosis present on baseline imaging
D-dimer test result after stopping anticoagulation

Physical examination
Height
Weight
O_2 Saturation
Heart rate
Respiratory rate
Temperature
Systolic blood pressure
Diastolic blood pressure
Crackles
Swelling of the whole leg
Redness of the leg
Warmth of the leg
Calf pain
Calf diameter of symptomatic leg
Calf diameter of asymptomatic leg
Superficial vein dilatation of the leg
Localized tenderness along the deep venous system
Pitting edema
Telangiectasia
Erythema
Varicose veins

Pigmentation
Eczema
Lipodermatosclerosis
Pretibial edema

ECG changes
ST changes
T wave changes

Chest x- ray
Parenchymal change
Band atelectasis
Elevation of hemidiaphragm

Laboratory test
D-dimer test
INR
INR values over the last 4 weeks
CRP (C-reactive protein)
pro – BNP (Brain natriuretic peptide)

Physician impression
Likelihood of recurrent DVT(%)
Likelihood of recurrent PE (%)
Another diagnosis more likely

Patient impression
Patient recognizes the symptoms from previous event(s)

Appendix E: Adjudication of Suspected Recurrent VTE Events

Recurrent VTE
Recurrent VTE will be excluded if participants have a low/intermediate or unlikely pre-test clinical probability with the Geneva or Wells rule and a negative D-dimer test result.

Recurrent Deep Vein Thrombosis
Recurrent DVT will be ruled out if participants have a normal ultrasound (fully compressible veins) or an unchanged/improved incompressible segment as compared with baseline when available.

The criteria for diagnosis of recurrent DVT will be:

1. Compression ultrasound revealing a new (compared to baseline/index ultrasound) area of non compressibility of a venous segment above the trifurcation of the popliteal vein will be considered diagnostic of a deep vein thrombosis.
   -OR-
2. Venography demonstrating a constant intraluminal filling defect in the deep veins above the trifurcation of the popliteal vein will be considered diagnostic of a deep vein thrombosis.

Recurrent Pulmonary Embolism
1. If the V/Q scan is normal or unchanged from baseline/index imaging, PE will be considered excluded.
2. If the V/Q scan is non-normal and a new unmatched segmental or greater perfusion defect is documented then recurrent PE will be diagnosed.
3. If a new matched or subsegmental perfusion defect is documented the test won't be considered positive for PE.
4. If participants receive a spiral CT scan and an intraluminal filling defect is seen in a segmental or greater vessel that was previously free of thrombus, pulmonary embolism is diagnosed. If the CT scan is normal or unchanged as compared with baseline, PE will be considered excluded.
5. Pulmonary angiography demonstrating a constant intraluminal filling defect or a cutoff of a vessel > 2.5 mm in diameter will be considered diagnostic for PE.

Death
All deaths during follow-up will be adjudicated as to the likelihood that the death was related to PE. The following criteria will be used: *Certain*: hypotension, hypoxia, cardiac arrest with no other explanation than PE, autopsy or radiographic confirmation; *Highly probable*: criteria for certain but another disease could have caused the death; *Probable*: other cause suspected based on clinical evidence but 100% certainty not available; *Unlikely*: all other cases.