A pilot study to assess feasibility of evaluating the safety and efficiency of a simplified diagnostic approach for pulmonary embolism

By

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Abstract

Background: Decision rules designed to reduce the need for pulmonary embolism (PE) imaging are seldom used by emergency physicians because of their complexity and poor credibility. We designed a simple, modified age-adjusted decision rule for PE testing in the emergency department (ED) – the 'Adjust-Unlikely' rule. Given increasing pressure on EDs, alternative methods to in-person recruitment are needed to validate the diagnostic performance of the Adjust-Unlikely rule in a full-scale study.

Objectives: The primary objective of this research was to assess the feasibility of a protocol consenting patients tested for suspected PE with the Adjust-Unlikely rule by telephone after they left the ED. The secondary objectives were to estimate safety and efficiency of the Adjust-Unlikely rule for diagnosing PE in the ED and to assess whether our methods introduced spectrum bias.

Methods: A prospective management pilot study was conducted in one ED and one urgent care centre. Adult patients tested for PE using the Adjust-Unlikely rule were recruited by telephone and followed for 90 days to identify subsequent testing for venous thromboembolism. PE and deep vein thrombosis (DVT) testing during follow-up was independently adjudicated. The feasibility outcomes were recruitment rate, missed eligible rate and overall follow-up rate. To assess for spectrum bias, multivariable logistic regression was used to compare included patients to missed eligible patients and patients who declined participation.

Results: Two hundred patients were included. On average, 9 patients were recruited per site, per week and 6 patients were missed per site, per week. The overall follow-up rate was 96.5%. Of the 143 patients with a negative Adjust-Unlikely rule on index visit, 1 patient was diagnosed with PE during follow-up. We found evidence of spectrum bias in our study population. Female patients and older patients were over-represented in our study population compared to patients who were eligible but not included.

Conclusions: Telephone recruitment did not meet our predefined thresholds for feasibility. This research has informed the design and planning of a full-scale study that will prospectively validate the safety and efficiency of the Adjust-Unlikely rule for diagnosing PE in the ED across Ontario.

Statement of Co-Authorship

All studies presented in this thesis are original works. Kerstin de Wit and Federico Germini derived the 'Adjust-Unlikely' rule for pulmonary embolism testing. Kerstin de Wit conceptualized the studies presented in this thesis. Nicole F. Morris and Natasha Clayton were responsible for obtaining ethics approval and overseeing the conduct of the studies. David Good provided the laboratory data used for participant screening and recruitment. Nicole F. Morris was responsible for participant recruitment, follow-up, data collection and data analysis, with contributions from Rasha Georgie and Elena Tataru. Sameer Parpia provided statistical support. Christine L. D'Arsigny and Paula James adjudicated all cases of venous thromboembolism testing performed in follow-up. Kerstin de Wit is the principal investigator for these studies. Nicole F. Morris prepared the manuscripts for publication. All co-authors consented to inclusion in this thesis.

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List of Abbreviations

Abbreviation	Definition
aOR	Adjusted odds ratio
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CT	Computed tomography
DVT	Deep vein thrombosis
ED	Emergency department
EMPET	Emergency Medicine Pulmonary Embolism Testing Study
HRT	Hormone replacement therapy
ICES	Institute for Clinical Evaluative Sciences
IQR	Interquartile range
OR	Odds ratio
PE	Pulmonary embolism
PERC	Pulmonary embolism rule-out criteria
SD	Standard deviation
VQ	Ventilation-perfusion

Chapter 1: General Introduction

1.1 What is pulmonary embolism?

Blood clots in the lungs are known as pulmonary embolism (PE). These clots typically originate in the legs as deep vein thrombosis (DVT) and travel to the lung vasculature.[1] Risk factors for PE include a previous history of PE or DVT, recent surgery, immobilization, and active cancer.[2] Still, up to 50% of first-time PEs are unprovoked.[3] Each year in Canada, PE is diagnosed in one in every 1000 people.[4] Many of these diagnoses are made in the emergency department (ED) using computed tomography (CT) pulmonary angiograms and ventilation-perfusion (VQ) scans. It is important to diagnose PEs quickly and accurately because without treatment, they can lead to permanent tiredness, breathlessness and death.[5] However, diagnosing PE can be challenging for emergency physicians because it is difficult to determine when to test.[6] Patients with PE commonly present with symptoms such as fatigue, chest pain, shortness of breath, dizziness, cough, fever, diaphoresis and hemoptysis,[7] which are non-specific and overlap with many other serious conditions.

1.2 Clinical decision rules

Clinical decision rules are evidence-based tools designed to help physicians quantify risk and make bedside diagnostic and therapeutic decisions. The rise of clinical decision rules in emergency medicine literature coincides with an increased demand for cost-effective and timely care.[7] Clinical decision rules can help emergency physicians cope with uncertainty and improve their efficiency[7] in this often overcrowded and overburdened environment. PE testing is the perfect example of a practice that can benefit from the application of a clinical decision rule because current practice is highly variable and highly inefficient.[8-11]

1.3 Existing clinical decision rules for PE testing

Several evidence-based clinical decision rules have been developed to standardize PE testing practices and reduce unnecessary diagnostic imaging for patients. They have demonstrated false negative rates of less than 2% (which is the generally accepted threshold for safety) and efficiencies (defined as the proportion of the patient population tested for suspected PE who does not require pulmonary imaging) of at least 40%.[12] Limiting diagnostic imaging is beneficial to avoid false positive PE diagnoses,[13] avoid nonsignificant incidental findings,[14] limit radiation exposure and ensure availability of emergency imaging for patients who most need it. Diagnostic imaging is also associated with longer ED stays,[15] which in turn contributes to ED overcrowding.

The 'pulmonary embolism rule out criteria' (PERC) rule was designed to exclude PE without the need for further testing in patients believed by their treating physician to be very unlikely to have PE.[16] In cases where the likelihood of PE is believed to be less than 15% and if no PERC criteria are present, PE can be safely ruled out without a further workup (see Figures 1.1 and 1.2).[16] When clinical suspicion of PE is thought to be greater than or equal to 15% or if any PERC[16] criteria are present, a clinical decision rule should be applied to guide the use and interpretation of blood D-dimer testing (see Figure 1.2).

D-dimer is fibrin degradation product generated from the proteolysis of cross-linked fibrin by plasmin.[17] Measuring the blood concentration of D-dimer is the most frequently used laboratory marker of coagulation and fibrinolysis activation.[17] In isolation, D-dimer is considered highly sensitive for detecting venous thromboembolism.[17] When compared to controls, the average blood D-dimer concentrations are increased 8-fold for patients with venous thromboembolism.[17] However, increased blood concentrations of D-dimer are seen for patients with any condition associated with enhanced fibrin formation and subsequent degradation by plasmin, resulting in lower specificity for detecting venous thromboembolism.[17] Additionally, small concentrations of D-dimer can be detected in the blood of healthy individuals, as 2-3% of plasma fibrinogen undergoes physiological conversion to fibrin and then degradation.[17] In order to further increase sensitivity and reduce the probability of missing a PE, testing guidelines support the integration of blood D-dimer testing with evidence-based strategies for calculating pretest probability.[17]

The Wells rule is a 7-item score that estimates the pretest probability of PE and was originally developed in 1998.[18] It has a maximum score of 12.5, with different points awarded for each clinical characteristic and patients classified as low, moderate or high risk for PE based on the points total (see Figure 1.1). [18] Since its derivation, the score has also been simplified to a 2-level pretest probability assessment, with risk classified as 'PE unlikely' or 'PE likely' based on the points total (see Figure 1.1).[19] When a D-dimer blood test is obtained, a result less than the manufacturer-recommended cut-off can be used to rule out PE without further diagnostic imaging in patients with a Wells[18] score of less than or equal to 4.0 (false negative rate, 0.13-0.69%, efficiency 37.5-42.1%) (see Figure 1.2).[12] Like the Wells[18] rule, the revised[20] and simplified[21] Geneva rules are scoring systems based on scales from 0.0-22.0 and 0.0-9.0 respectively, with a score of 10 or less indicating low to intermediate clinical probability for the revised Geneva score and a score of 4 or less indicating low to intermediate clinical probability for the simplified score (see Figure 1.1). According to these rules, patients deemed low to intermediate clinical probability can also have PE safely ruled out using the manufacturer recommended cut-off for blood D-dimer levels (false negative rate, 0.4-1.2%, efficiency 28.8-30.5%) (see Figure 1.2).[12]

The cut-off value for the D-dimer blood test is, itself, a topic of study, with the threshold used to exclude the diagnosis of PE varying from the manufacturer recommended cut-off (typically 500 ng/ml[22]), 1,000 ng/ml[23,24] and 'age-adjusted' (age x 10 for patients > 50 years).[21,25-27] The YEARS algorithm, for example, was derived from the three items most predictive of PE on the Wells rule[28] (see Figure 1.1) and modifies the D-dimer threshold to rule out PE without imaging depending on whether any of these three items are present (see Figure 1.2).[23] van der Hulle and colleagues found that PE can be safely excluded in patients without YEARS items and a D-dimer result less than 1000 ng/ml or with one or more YEARS items and a D-dimer less than 500 ngl/ml (false negative rate, 0.6%, efficiency 48.0%).[23] Similarly, the PEGeD study demonstrated that PE could be safely ruled out in patients with a Wells[18] score of 4.0 or less and a D-dimer of less than 1000 ng/ml and in patients with a Wells[18] score between 4.5 and 6 and a D-dimer of less than 500 ng/ml (see Figure 1.2).[24] Additionally, researchers for the ADJUST-PE studies demonstrated that the age-adjusted D-dimer threshold can be used to safely rule out PE in patients older than age 50 classified as having low, intermediate or unlikely clinical probability according to either the Wells,[18] simplified[21] or revised[20] Geneva scores (false negative rate, 0-0.3%, efficiency, 41.1-54.6%) (see Figure 1.2).[21,25]

Pulmonary embolism rule out (PERC) criteria		
Clinical characteristic	**PERC negative**	**PERC positive**
Age ≥ 50 years	No to all	Yes to any
Heart rate ≥ 100 beats/min		
Swelling in one leg		
Hemoptysis		
Surgery or trauma within past 4 weeks		
Previous PE or DVT		
Hormone use		
Oxygen saturation < 95% on room air		

Geneva Score		
Clinical characteristic	**Revised Points**	**Simplified Points**
Heart rate ≥ 95 beats/min 75 – 94 beats/min	 5.0 3.0	 2.0 1.0
Pain on lower limb deep vein palpitation and edema in one leg	4.0	1.0
Previous DVT or PE	3.0	1.0
Pain in one lower limb	3.0	1.0
Hemoptysis	2.0	1.0
Surgery or fracture within previous month	2.0	1.0
Active cancer	2.0	1.0
Age > 65 years	1.0	1.0
Probability assessment		
Low risk for PE	0.0 – 3.0	0.0 – 1.0
Intermediate risk for PE	4.0 – 10.0	2.0 – 4.0
High risk for PE	≥ 11.0	≥ 5.0

Wells score	
Clinical characteristic	**Points**
PE is the most likely diagnosis	3.0
Signs and symptoms of DVT	3.0
Heart rate > 100 beats/min	1.5
Immobilization for > 3 days or surgery within previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Active cancer	1.0
3 level probability assessment	
Low risk for PE	< 2.0
Moderate risk for PE	2.0 – 6.0
High risk for PE	> 6.0
2 level probability assessment	
PE unlikely	≤ 4.0
PE likely	> 4.0

YEARS items		
Clinical characteristic	**Meets criteria**	**Does not meet criteria**
PE is the most likely diagnosis	No to all	Yes to any
Hemoptysis		
Clinical signs of DVT		

Figure 1.1 Different clinical decision rule items and scoring systems

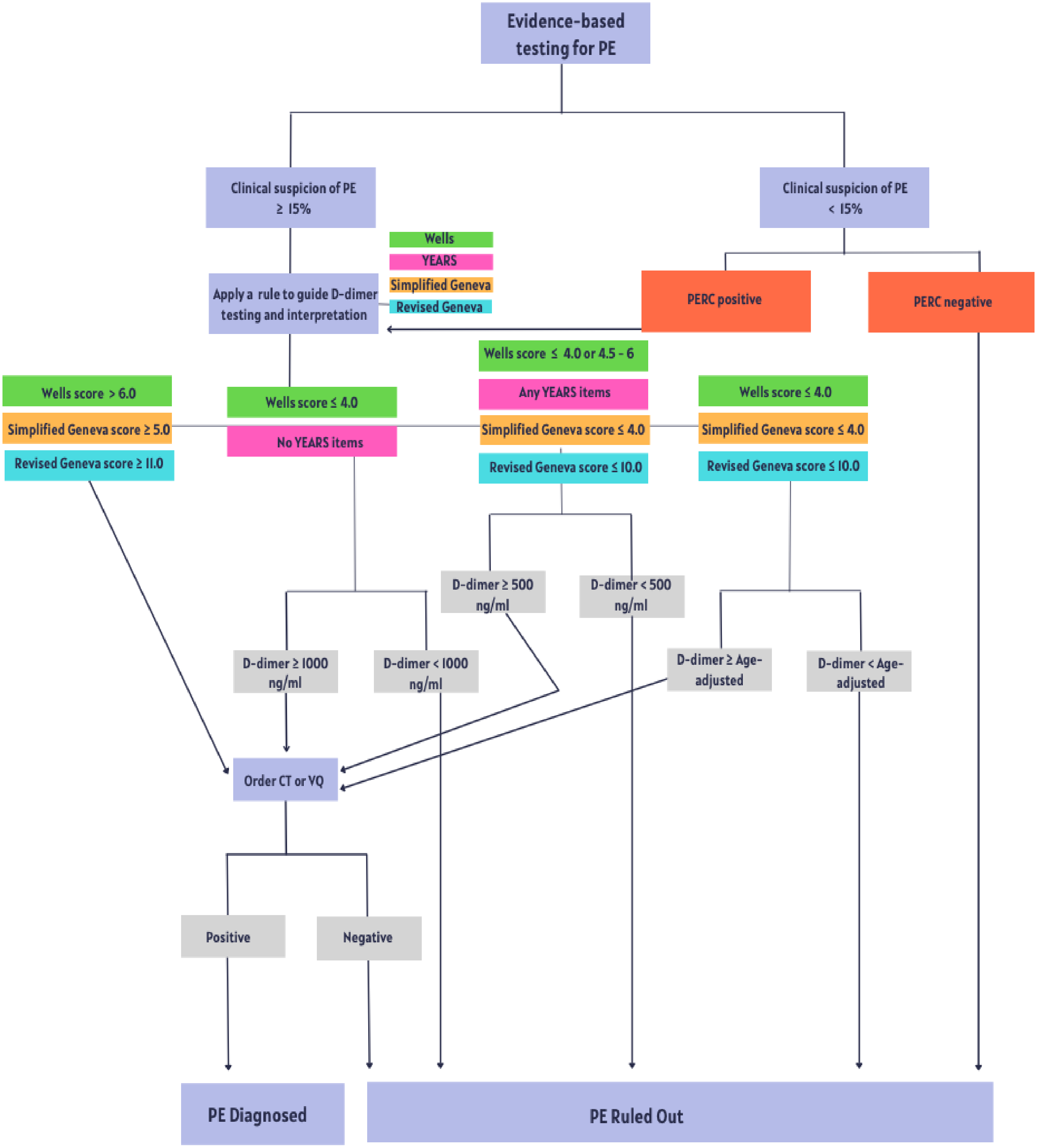


Figure 1.2 Different evidence-based approaches to testing for PE

1.4 Previous knowledge translation and implementation efforts

Despite advancements in PE clinical decision rule derivation and validation research, gaps remain in the knowledge translation and implementation of these diagnostic strategies into everyday clinical practice. Many studies have investigated interventions aiming to standardize PE testing practices and promote physician adoption of previously validated clinical decision rules such as the Wells,[29-48] PERC,[29,31,36,38,45,48,49] and revised Geneva[49,50] rules in the ED. Most commonly, these interventions have involved the implementation of electronic decision support tools in the form of desktop applications, electronic medical record modifications and additions such as pop-up windows and alerts.[29-33,35-37,43-47,49,50] Educational interventions such as lectures and grand rounds presentations, emails and the distribution of materials such as posters, handouts and stickers have also been used to promote awareness of the evidence associated with existing clinical decision rules and international PE testing guidelines, and to promote the uptake of new protocols and decision support tools.[36,38,40-42,45,46,49] Some researchers have also distributed benchmarking reports comparing the rates of CT pulmonary angiogram use across the department and personalized feedback pertaining to individual use patterns.[31,34,38,45]

The observed impacts of these strategies on CT pulmonary angiogram use and diagnostic yield have varied greatly across the literature. Some studies have reported statistically significant reductions in the proportion of CT pulmonary angiograms ordered[32,36,44-46] and increases in diagnostic yield[30,33,45-47] in post-intervention periods. For example, Jiménez and colleagues observed a 6.3% decrease ($p=0.02$) in the use of CT pulmonary angiogram use for suspected PE following the implementation of their electronic decision support tool that required obtaining a blood D-dimer test and mandatory calculation of the Wells[18] score for patients with suspected PE.[44] Similarly, Redinger and colleagues observed a 9.25% increase in diagnostic yield following the implementation of a pop-up tool in the electronic medical record that 'triggered' when physicians attempted to order a CT pulmonary angiogram for suspected PE (p=0.001).[47] All physicians were required to calculate the Wells score[18] prior to placing their order.[47] There was no option to dismiss the pop-up or avoid data entry, but physicians were still permitted to place their order, regardless of the patient's calculated pretest probability or recommendations from the tool to follow a different testing pathway or cancel the order.[47] In contrast, many other studies investigating the impact of electronic clinical decision support tools have not observed any statistically significant improvements in imaging use[30,31,35,37] or yield.[31,36-38,43]

In cases where reductions in imaging use and increases in diagnostic yield have been reported, the results may be limited by the variability observed in physician adoption of the interventions. For example, Bledsoe and colleagues found an 11.5% increase in diagnostic yield (p<0.001) when providers engaged with a desktop application for the calculation of PERC[16] and revised Geneva[20] scores.[49] However, they found that the application was launched for only 5.2% of eligible patient encounters.[49] Four other studies reported adoption between 29%-45% following the implementation of their interventions aimed at promoting clinical decision rule use.[31,39,42,48] It is equally important to consider that even when clinical decision rules are applied, physicians may not adhere to their recommendations for further PE testing. Some researchers have measured the impact of interventions on physician adherence.[29,31,33,34,36,41,43] Of these studies, only one demonstrated physician adherence above 80%.[34] Prior to study launch, Raja and colleagues modified the process for ordering imaging for suspected PE in the electronic record at their ED, such that physicians had to input a patient's D-dimer result (or indicate that the test was not ordered) and their clinical suspicion of PE (high, intermediate or low).[34] The support tool then offered recommendations according to the Wells[18] score based on physician inputs.[34,46] Physicians could choose to cancel their imaging order or ignore the recommendations.[34,46] When researchers studied the impact of distributing randomized individual and anonymized group data on physician adherence to this study protocol, they found that adherence increased from 78.3% to 85.2% in the group that received feedback reports ($p<0.05$) and remained unchanged in the control group that did not receive feedback (78.8% to 77.2%, $p=0.5$).[34]

Notably, there is a paucity of research on the long-term impacts of interventions aiming to standardize PE testing practices and promote physician adoption of previously validated clinical decision rules, and whether positive initial results have been sustained over time. Despite knowledge translation and implementation efforts, the prevalence of PE in North American patients tested has remained stable for two decades.[51] In Canada, PE is diagnosed in only 8% of emergency patients who are tested for it.[51]

1.5 Barriers to clinical decision rule adoption

Following the implementation of their clinical decision support tools, three studies also collected and reported on qualitative data pertaining to physician decisions to use or not to use the clinical decision rule being targeted when testing for PE.[29,39,48] The most commonly reported reasons for physician non-adherence were added time and interruptions to clinical workflow.[29,39,48] Salwei and colleagues implemented an electronic clinical decision support tool directly into the electronic medical record that calculated PERC[16] and Wells[18] scores, as applicable, for patients with suspected PE.[48] When researchers surveyed physicians on real-time use in the ED, they reported that the tool took too long to locate on the ED software system and too long to fill in.[48] Some physicians suggested that this may be improved if more clinical variables could ‘auto-populate’ based on other available information in the patient’s electronic medical record.[48] The clinical decision support tool implemented into the electronic medical record by Goehler and colleagues was also designed to avoid redundancy by retrieving and auto-populating heart rate and oxygen saturation from the electronic medical record.[29] Despite these efforts, time constraints were still cited as a reason for lack of adherence, and only 4% adherence to testing pathways according to the tool’s calculated PERC[16] and Wells[18] scores was observed.[29] Though not a specific outcome measure in their interventional study, Drescher and colleagues reported that emergency physicians at their ED requested that the modifications made to the D-dimer and CT pulmonary angiogram order processes in the electronic medical record (such that calculating a Wells[18] score was mandatory prior to placing the order) be removed at the end of the study period.[33] Physicians reported that the tool was too time consuming to use and that they did not believe clinical decision aids were helpful.[33]

These findings align with a qualitative study conducted by our own research group that sought to better understand emergency physician choices in testing patients for suspected PE in the ED.[6] In 2021, Zarabi and colleagues conducted in-depth interviews with emergency physicians across Canada and found that many physicians believe existing clinical decision rules are too time consuming, too complex and require too great a cognitive demand to apply during busy shiftwork.[6] Additionally, physicians reported preferences for clinical gestalt and imaging over bedside tests.[6] These findings are also consistent with the ‘Ten commandments for effective clinical decision support’ proposed by Bates and colleagues.[52] According to this report, effective decision making tools should optimize integration with existing physician workflow.[52] They should be simple, fast to apply and request minimal information.[52] Taken together, there is evidence to suggest that the gap in standardization of practice for PE testing in the ED could be due to flaws in the design of the existing clinical decision rules, rather than flaws in the designs of previously trialed knowledge translation strategies and interventions aiming to promote their use. Emergency physicians could benefit from a clinical decision rule designed to align with their preferences and the specific demands of the ED.

1.6 Developing the 'Adjust-Unlikely' clinical decision rule

Using qualitative physician interviews and a sequential diagnostic evaluation process,[6,53] we have designed and validated a new decision rule for PE testing in the ED – the 'Adjust-Unlikely' rule.[54] The Adjust-Unlikely rule is simple, fast to use and can be easily integrated into physician workflow. To date, it is the only PE testing rule designed specifically to align with the ED environment and physician needs. At the first stage of this work, we implemented 'D-dimer-only' PE testing at Hamilton Health Sciences Centre.[55] Among the 2578 patients with D-dimer less than 500 ng/ml, no cases of PE were diagnosed in the subsequent 30 days.[55] The Adjust-Unlikely rule builds on the D-dimer-only testing approach by allowing emergency physicians to use clinical gestalt, the strongest predictor item of PE in the Wells[12] score,[56] to determine the threshold for a negative D-dimer. When PE is not the most likely diagnosis, PE can be excluded with a D-dimer result less than the age-adjusted threshold and when PE is the most likely diagnosis, PE can be excluded with a D-dimer result of less than 500 ng/ml (see Figure 1.3). We previously proved the safety of the Adjust-Unlikely rule in our recent diagnostic accuracy study, where the rule was found to be 100.0% sensitive (95% confidence interval (CI) 97.2, 100.0%).[54]

While this prior research has demonstrated that Adjust-Unlikely testing for suspected PE is safe, in general, emergency physicians look for external validation across multiple sites before implementing a new PE test. Emergency physicians are anxious about missing PE because on occasion PE can be fatal.[6] Larger-scale research published in high-impact journals is needed for confident adoption of new PE testing protocols. Therefore, as a next step, we plan to prospectively validate the safety of the Adjust-Unlikely rule in a multicentre study at EDs across Ontario. We will align the future study with prior research where PE testing performance is reported in terms of safety (defined as the 90-day false negative rate) and efficiency (defined as the proportion of the population tested for PE who avoid PE imaging).[12] Because emergency physicians are focused on safety of PE testing, the primary outcome for the full study will be safety.

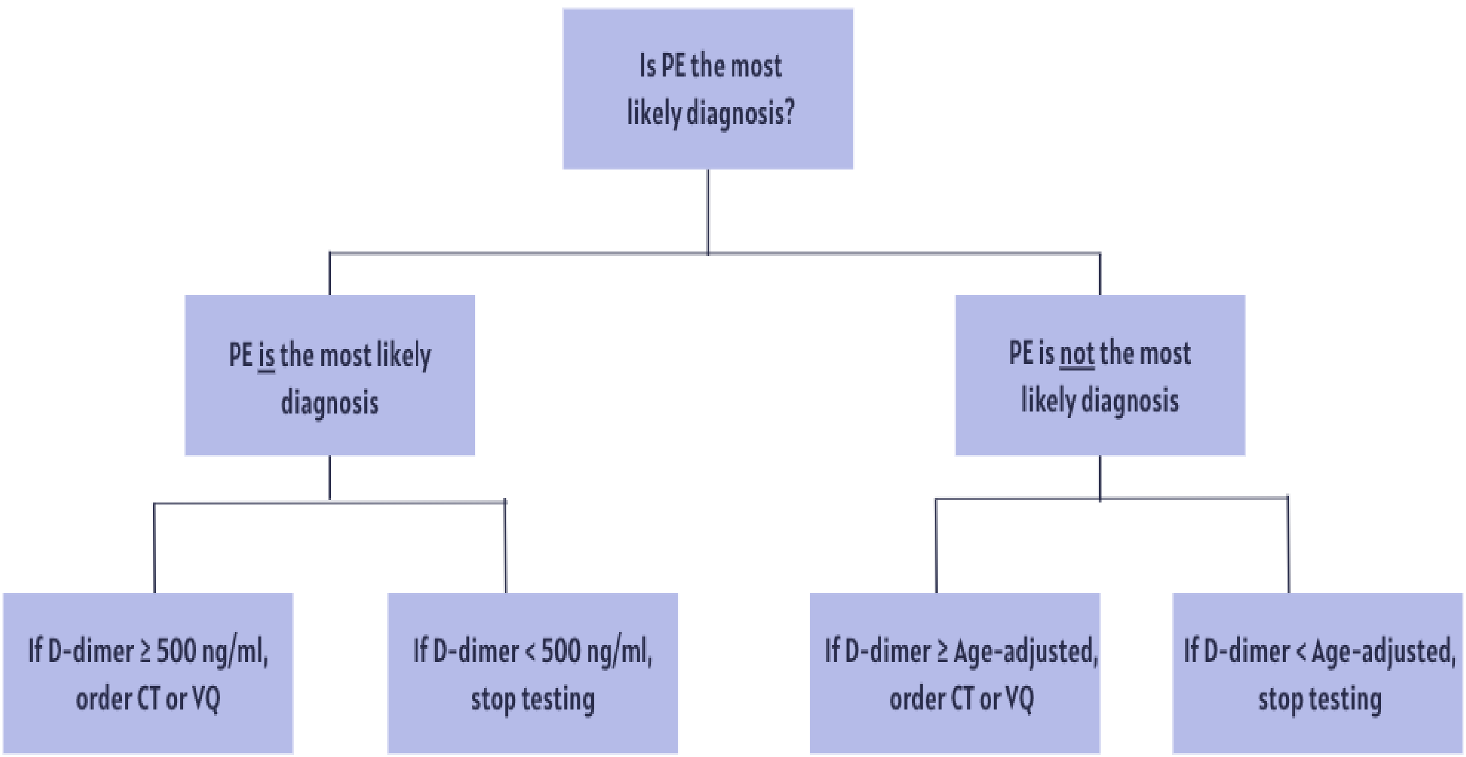


Figure 1.3 The Adjust-Unlikely rule for PE testing

1.7 Pilot study definition and utility

Pilot studies are a key step in the design, planning and implementation of many great undertakings in clinical research. Typically, they are conducted with the purpose of assessing the feasibility of a proposed study protocol intended for use in a larger scale study.[57] In addition to helping researchers determine the appropriateness of their research question,[58] screening, recruitment, loss to follow-up, data collection and management are all aspects of feasibility that can be quantified and examined with a pilot study.[57,59-61] By predefining target measurements that would prove the feasibility of a pilot study's approach, researchers are provided with the opportunity to refine and modify study procedures that do not meet these targets, as necessary, before scaling up.[57] Prior diagnostic ED pilot studies which demonstrated feasibility[62,63] went on to successful full studies.[55,64] Specific to PE diagnostic research, for example, Germini and colleagues published their pilot study assessing feasibility of implementing an evidence-based PE diagnosis protocol at three Ontario EDs.[62] This study served as the critical first step in the successful implementation of the 'D-dimer for all' PE testing approach in two EDs at Hamilton Health Sciences Centre, which was ultimately met with 97.6% adherence in the full study.[55] In addition to helping researchers to inform the full study, pilot studies generate important preliminary data that can be used to secure funding for the future research. In today's time, national funding bodies such as the Canadian Institutes of Health Research (CIHR) encourage the support of pilot data on grant applications.[65]

Pilot studies also allow for the identification of practical problems, giving an opportunity to address these problems in a low-stakes study. Sometimes, a pilot study might demonstrate that a study cannot be conducted which avoids future wastage of grant funds. Given the potential for positive results bias in the publication of pilot studies, it is difficult to discern the proportion of pilot studies conducted that are found not to demonstrate feasibility and subsequently, do not progress to full studies. A systematic review of pilot studies undertaken in palliative care research, for example, found that of the 56 included articles in the review, only two studies reported that their research designs were not feasible.[66] Even when feasibility is demonstrated, authors do not always explicitly report on whether the full study is being conducted, or will be conducted. The same review article reported that of the 48 studies that found their study designs were feasible, the intention to progress the research to a full study was only explicitly stated in seven studies.[66] Similarly, a review on pilot studies published in the journal of *Clinical Rehabilitation* found that of the 191 studies published between 1987 and 2015, only 30 were either followed by a definitive clinical trial or had the full study protocol published/the full study in progress.[67]

1.8 Pilot study rationale

The ED is a specific example of a research environment that can benefit from the pilot study. Recruiting emergency patients into research must take into account challenges such as overcrowding, time pressures and the 24-hour nature of emergency medicine. One method that may prove feasible is consenting emergency patients for study participation by telephone after they leave the ED. Although most previous diagnostic PE research recruited study participants in-person, prior to being tested with the clinical decision rule under investigation,[16,18,21] delayed telephone consent has been shown to be a feasible and well-accepted method for recruitment in other areas of emergency medicine research.[68-71] For example, in a study on medication compliance, Campbell and colleagues successfully obtained consent to collect follow-up data from 71% of eligible patients via telephone after their ED discharge.[69] Compared to patients who provided in-person consent to collect follow-up data during their ED visit, there were no statistically significant differences in the proportion of eligible patients who refused participation between groups.[69]

Additionally, the primary outcome for most diagnostic PE studies is the proportion of patients who test negative for PE and are subsequently diagnosed with PE or DVT in the following three months. Follow-up is typically performed using both medical record review and contact with the study participant or family physician. However, it is unclear if we could achieve a high telephone follow-up rate in the current climate of unwanted or spam calls. Performing a pilot study will allow us to assess the feasibility of a study protocol consenting and following-up with patients by telephone.

1.9 Spectrum bias definition and examples from the literature

The pilot study will also help us to determine if this method introduces spectrum bias, a phenomenon that has not been explored in recent PE diagnostic research. Spectrum bias occurs when a study population does not reflect all types of patients and presentations encountered in everyday clinical practice.[72] In past PE studies, it was not standard practice to report the proportion of patients eligible for participation who were not included in the study population or compare their demographics to those of the study population. We do not know how the processes for eligibility screening and in-person recruitment introduce spectrum bias. Rutjes and colleagues analyzed the direction and magnitude of the effects of potential sources of bias and variation in 31 meta-analyses evaluating 487 primary studies on different diagnostic tests and found that studies that did not enroll patients consecutively reported significantly higher estimates of diagnostic accuracy compared to studies involving consecutive patient enrollment.[73] Similarly, an earlier study examining 11 meta-analyses evaluating the diagnostic accuracy of 184 studies on different diagnostic tests showed that study participants nonrepresentative of clinical populations tended to overestimate diagnostic performance.[74]

With respect to emergency medicine research, studies evaluating point-of-care ultrasound for DVT diagnosis have been used to illustrate the potential effects that spectrum bias can have on the reporting of diagnostic accuracy.[75-77] For example, Kohn and colleagues compared two studies[78,79] showing that point-of-care ultrasound is 100% sensitive and 91.8-100% specific relative to the gold standard conducted by radiologists, to a third similar study[80] showing only 70% sensitivity and 89% specificity. The authors described that whereas the first two studies[78,79] used convenience sampling and may have excluded patients with indeterminate test results, the third study[80] enrolled patients consecutively and included those with indeterminate test results.[77] The authors suggest that if a disproportionate number of excluded patients with indeterminate test results were subsequently diagnosed with DVT (which may have been classified as false negatives had they been included in the study) or had DVT ruled out (which may have been classified as false positives), this could explain the higher sensitivity and specificity observed.[77] Conversely, in part two of their series on sources of bias in studies on diagnostic test performance for the *Emergency Medicine Journal*, Kea and colleagues highlight a study on point-of-care ultrasound for DVT where investigators categorized indeterminate exams as positives for DVT,[81] which the authors suggest potentially increased the number of false positives reported and ultimately decreased reporting of the test's specificity.[76]

There is also evidence to suggest that differences in disease spectrum can affect reporting on the diagnostic accuracy of strategies to test for PE in the ED. In 2011, Hugli and colleagues conducted a retrospective study to externally validate the performance of the PERC[16] rule in a cohort of emergency patients with suspected PE across six EDs in Switzerland, France and Belgium.[82] The authors found that PE was diagnosed in 5.4% of patients who, according to the rule, would have been classified as 'PERC negative'[16] and had PE ruled out without further testing.[82] This finding contradicts earlier validation studies conducted in North America, where PERC[16] was found to have a false negative rate of 0-1%.[16,83,84]

In general, European studies report a prevalence of PE in emergency patients four times the prevalence of PE reported in studies on North American emergency patients tested for PE.[51] Higher prevalence may signal more selective testing for PE, which could explain why the PERC[16] rule cannot safely identify low risk patients and rule out PE in this clinical population. Because the negative likelihood ratio for the PERC rule remains relatively fixed, if the pretest probability of PE is too high in European patients, the post-test probability will still be too high to safely exclude PE.

It is also possible that European patients tested for suspected PE present with more obvious or severe symptoms, which helps to explain the higher sensitivity and lower specificity reported for other clinical decision rules, when studied in European versus North American patients.[12] In their individual patient data meta-analysis, Geersing and colleagues found that a combined diagnostic strategy to rule out PE using the PERC[16] rule and a Wells[18] score of 4.0 or less had a sensitivity of 95.7% and a specificity of 22.2% in American EDs, compared to 97.7% sensitivity and 12.0% specificity in European EDs.[12] The finding that higher prevalence is associated with higher sensitivity and lower specificity was also published recently by a study analyzing 6909 studies of diagnostic test accuracy in the *Canadian Medical Association Journal*.[85]

These observed differences, although small, offer important insights for providers looking to apply the results of research to their own clinical populations. The higher the probability of PE, the lower the test negative likelihood ratio must be to produce clinically meaningful results. It is important to assess for spectrum bias in our own study population because if we find that the characteristics of those who are included in the study are significantly different from those who were eligible but could not be contacted, refused participation, or were excluded by a list of predefined criteria, the effect is the potential misrepresentation of the Adjust-Unlikely rule performance in the full study. Ultimately, the consequences would be misinformed rule out or else discarding of a rule which could be clinically helpful.

1.10 Study overview

The aim of this pilot study was to assess the feasibility of a study protocol recruiting emergency patients tested for suspected PE using the Adjust-Unlikely rule by telephone, and successfully following them for 90 days to identify subsequent diagnoses of venous thromboembolism. These results will be used to inform the planning of our full study, which will prospectively evaluate the safety and efficiency of the Adjust-Unlikely rule for diagnosing PE in the ED.

The primary outcomes assessing feasibility were the recruitment rate (per site, per week), the missed eligible rate (per site, per week), and the overall follow-up rate. Secondary outcomes were the safety of the Adjust-Unlikely rule for diagnosing PE in the ED (the proportion of enrolled patients who tested negative for PE with Adjust-Unlikely at initial assessment and were subsequently diagnosed with DVT or PE during the 90-day follow-up), efficiency (the proportion of all patients who tested negative with the Adjust-Unlikely rule), and a comparison of missed eligible patients and those who declined, and excluded patients to study participants (assessing for spectrum bias).

We hypothesized that we would be able to recruit at least 5 patients per site, per week, miss (unable to contact) no more than 2 eligible patients per site, per week, and successfully follow-up with at least 90% of included patients by telephone, text, or email at 90 days. The target sample size for the pilot study was 200 patients. Assuming a post-test probability of 1% and an estimated 40% of participants testing negative using the Adjust-Unlikely rule, the sample size would yield a 95% CI of 0.1% to 7.7% for the false negative rate (which is the primary outcome of the full study).

1.11 Approach

This thesis addresses the above objectives in chronological order. Chapter 2, in manuscript form, presents the primary outcome assessing feasibility and secondary outcomes estimating the safety and efficiency of the Adjust-Unlikely rule for diagnosing PE in the ED. Chapter 3, in manuscript form, presents the secondary outcome assessing for spectrum bias in our study methods. Chapter 4 includes a general discussion of our findings and concludes with a discussion on the potential implications of, and future directions for this research.

Chapter 2: A pilot study to assess feasibility of evaluating the safety and efficiency of a simplified diagnostic approach for pulmonary embolism

2.1 Abstract

Background: Prior pulmonary embolism (PE) diagnostic studies recruited emergency department (ED) patients at the time of testing. This recruitment method is increasingly impractical given pressures on EDs. Alternative recruitment strategies are needed. The aim of this study was to assess the feasibility of a protocol consenting patients for an ED PE testing study by telephone.

Methods: This was a prospective pilot study conducted in one ED and one urgent care centre in Ontario, Canada. Adult patients tested for PE using the Adjust-Unlikely rule were consented to participate by telephone after leaving the ED. Patients were followed for 90 days by chart review plus telephone, text or email to identify subsequent testing for venous thromboembolism. PE and deep vein thrombosis (DVT) testing during follow-up was independently adjudicated. The feasibility outcomes were recruitment rate, missed eligible rate and overall follow-up rate.

Results: From a total of 684 patients between March 24, 2023, and June 10, 2023, 210 were excluded and 474 were eligible for recruitment. 200 patients were recruited. The median age was 58, 72.2% were female, 12.6% had a prior history of venous thromboembolism, 8.1% took anticoagulant medication, 4.5% had cancer and 3.5% were diagnosed with PE on index visit. The recruitment rate averaged 9 patients per site, per week (SD 5.7) and the missed eligible rate averaged 6 patients per site, per week (SD 3.5). After 90 days, 2 patients withdrew and 191/198 (96.5%, 95% CI 92.9, 98.3%), had been contacted in follow-up. 143/198 (72.2%) participants

did not require pulmonary imaging because PE was excluded by Adjust-Unlikely. 1/143 (0.7%, (95% CI 0.1, 3.9%) of these patients was diagnosed with PE in the segmental pulmonary arteries during 90-day follow-up.

Conclusions: Recruitment by telephone did not meet our predefined thresholds for feasibility as the missed eligible rate was high. There was minimal loss to follow-up.

2.2 Introduction

Pulmonary embolism (PE) testing in the emergency department (ED) is not standardized in Canada. Choosing Wisely Canada states that emergency physicians should not obtain diagnostic imaging for PE until a decision rule has been applied and where necessary, D-dimer obtained. We designed a simple, modified age-adjusted decision rule for PE testing in the ED – the 'Adjust-Unlikely' rule.[54] Adjust-Unlikely combines the use of D-dimer testing for all patients with the treating physician's judgement about whether or not PE is the most likely diagnosis. The age-adjusted D-dimer cut-off is used to rule out PE when PE is not the most likely diagnosis, and the standard manufacturer-recommended cut-off is used when PE is the most likely diagnosis. Our prior research on the Adjust-Unlikely rule is limited to one diagnostic accuracy study, where it was found to be 100.0% sensitive (95% confidence interval (CI) 97.2, 100.0%).[54] We plan to prospectively evaluate the safety and efficiency of the rule for diagnosing PE in the ED.

Prior PE testing validation studies have consented patients at the time of testing for suspected PE.[16,18,24,25,27] EDs are overcrowded, there is a lack of privacy, and many patients are assessed at night. Research assistants are seldom present in the ED 24 hours a day. Previous PE testing validation studies were slow to recruit. For example, in the multicentre evaluation of the safety of the Wells rule, less than 2 patients were recruited per site, per week, from five Canadian hospitals.[18] In the YEARS study, recruitment rate averaged just over 3 patients per site, per week, from 12 hospitals in the Netherlands.[23] Similarly, in the prospective validation of an age-adjusted D-dimer cut-off involving 19 hospitals across four European countries in 2014, an average of just over 1 patient was recruited per site, per week.[25] Building on this work, researchers conducted a further validation study at 10 hospital sites across three European countries in 2021, where recruitment rate averaged less than 1 patient per site, per week.[27] However, in Canadian EDs, 5 to 15 patients are tested for PE on a daily basis, suggesting the missed eligible rate of prior studies may have been high.[86]

The primary outcome for most diagnostic PE studies is the rate of PE or deep vein thrombosis (DVT) diagnoses among patients with negative PE testing over the following three months. Conventionally, follow-up is performed using both medical record review and contact with the patient or family physician. When too many participants are lost to follow-up, the validity of the study findings can be called into question. Recent PE testing studies report successful 3-month follow-up rates of between 98.7% and 99.9%.[23-25,27] However, given the frequent nature of telemarketing and unwanted or spam calls, people are less likely to answer the telephone in today's time. It is unclear if we could achieve a high telephone follow-up rate in the current climate.

The aim of this pilot study was to assess the feasibility of recruiting emergency patients tested for suspected PE using the Adjust-Unlikely rule by telephone, and successfully following them for 90 days to identify subsequent diagnoses of venous thromboembolism.

2.3 Methods

2.3.1 Study Design and Setting

This was a prospective management pilot study involving patients who were tested for suspected PE in one ED and one urgent care centre in Kingston, Ontario, Canada. The study was approved by Clinical Trials Ontario (Project ID 4269).

2.3.2 Selection of Participants

Patients were eligible for inclusion if their emergency physician tested them for PE. Exclusion criteria were age less than 18, PE testing without using the Adjust-Unlikely rule, the physician being aware of the D-dimer level before assessment of whether PE was the most likely diagnosis, a new indication for anticoagulation on assessment (other than PE), inaccessibility for follow-up (defined as patients living in long-term care or nursing homes, incarcerated, unhoused and/or without a reliable telephone number in their medical record), expired patients, patients with repeat visits who were previously deemed eligible but declined participation, and patients who had previously participated in the study.

2.3.3 PE Testing Process

Physicians followed the Adjust-Unlikely rule for PE testing (Figure 2.1). When emergency physicians ordered D-dimer testing for suspected PE, they recorded whether PE was the most likely diagnosis or not. If PE was not the most likely diagnosis, at the time of order they were prompted to exclude PE without imaging if the D-dimer result was less than the age-adjusted threshold (age x 10). If PE was the most likely diagnosis, at the time of order they were prompted to exclude PE with a D-dimer result of less than 500 ng/ml FEU. This protocol was implemented at both sites in December 2022 when all physicians were educated on the process at department rounds, through online videos and voice recordings linked to the department newsletter and posted in the department WhatsApp group chat.

2.3.4 Participant Recruitment

Eligible patients were identified by reviewing patients who had a D-dimer blood test, computed tomography (CT) pulmonary angiogram or ventilation-perfusion (VQ) scan ordered in the ED or urgent care centre during the study period. A manual chart review was conducted to identify patients who met exclusion criteria. Patients deemed eligible for participation after these initial screening steps then received a phone call to ask for their consent to participate. Three call attempts were made per eligible patient, during the weekday, evening, and weekend.

2.3.5 Adjust-Unlikely Testing Results

Physicians had to record whether PE was the most likely diagnosis or not when they ordered a D-dimer blood test in the electronic medical record. Research assistants extracted these data from the D-dimer order in the electronic medical record.

2.3.6 90-day Follow-up

The electronic medical record was reviewed to identify new venous thromboembolism testing during the 90-day follow-up period at the two hospitals. Patients were also contacted again by telephone, text and/or email (depending on their state preference) after 90 days to check if they had been tested for venous thromboembolism at another hospital during the follow-up period. If patients indicated that they were tested at another hospital, signed written permission was collected to obtain copies of scan reports. An independent adjudication committee reviewed all venous thromboembolism testing within 90 days. The adjudication committee reviewed any deaths during follow-up, classifying the cause of death according to the International Society of Thrombosis and Haemostasis.[87] The adjudication committee consisted of two physicians (a respirologist and hematologist) who were blinded to the initial Adjust-Unlikely assessment. Disagreements were resolved by consensus.

2.3.7 Data Collection

Patient age, sex, date of presentation, triage vital signs, anticoagulation use, D-dimer, imaging results, and disposition were extracted from the medical record. Data on prior history of PE and/or DVT, oral contraceptive or hormone replacement therapy (HRT) use, and venous thromboembolism risk factors were obtained via self-report during the initial telephone interview and extracted from the medical record. A positive in either source was counted as positive.

2.3.8 Analysis

The primary outcomes assessing feasibility were the recruitment rate (per site, per week), the missed eligible rate (per site, per week), and the follow-up rate overall.

Secondary outcomes were aligned with prior PE testing research:[12] the safety of the Adjust-Unlikely rule for diagnosing PE in the ED (the proportion of enrolled patients who tested negative for PE with Adjust-Unlikely at initial assessment and were subsequently diagnosed with DVT or PE during the 90-day follow-up) and efficiency (the proportion of all patients who tested negative with the Adjust-Unlikely rule). A priori, a diagnosis of PE in follow-up was defined as the finding of a new central filling defect within the main, lobar, segmental or more than one subsegmental pulmonary artery on CT, a high probability planar VQ scan, or VQ-SPECT showing perfusion mismatch at the lobar, segmental or more than one subsegmental pulmonary arteries. A diagnosis of DVT in follow-up was defined as the findings of new incompressibility of a leg vein between the calf trifurcation and the inferior vena cava.

Follow-up, venous thromboembolism diagnosis during follow-up and rule efficiency were reported as proportions and 95% CIs were calculated using the Wilson Score method. We predefined our sample size as 200 patients which would be sufficient to determine weekly recruitment and missed eligible rates. Based on current PE testing rates in Canadian EDs and prior diagnostic PE study recruitment rates, a priori we set feasibility at recruitment of 5 participants per site, per week, with a missed eligible rate of no more than 2 patients per site, per week, and a successful follow-up rate of at least 90% of enrolled patients. Analysis was conducted using SPSS version 29.

2.4 Results

2.4.1 Characteristics of Study Participants

Six hundred eighty-four patients were tested for PE between March 24, 2023 and June 10, 2023. A total of 210 patients were excluded (see Figure 2.2). From 474 eligible patients, 200 were recruited, 127 were missed (could not be contacted) and 143 declined participation. Three patients lacked the capacity to consent and one patient could not be consented as they did not speak English. The median age of included patients was 58, 72.2% were female, and 3.5% were diagnosed with PE on index visit. Table 2.1 displays the characteristics of included patients.

Table 2.1 Characteristics of included patients

Description	Number (%) or median (IQR) N= 198
Demographic information	
Age (years)	58 (40.8-69.3)
Female	143 (72.2)
BMI (kg/m^2)	27.2 (23.4-31.9)
Anticoagulation use	16 (8.1)
Oral contraceptive or HRT use	30 (15.2)
Pregnancy in past year	2 (1.0)
Trauma in past 8 weeks	0 (0)
Hospital admission in past 8 weeks	10 (5.1)
Surgery in past 8 weeks	6 (3.0)
History of cancer	9 (4.5)
History of PE or DVT	25 (12.6)
Upper or lower limb paralysis or paresis	5 (2.5)
Emergency department presentation time	
Day (8:01 am to 5:00 pm)	125 (63.1)
Evening (5:01 pm to 12:00 am)	50 (25.3)
Night (12:01 am to 8:00 am)	23 (11.6)

Description	Number (%) or median (IQR) N= 198
Vital signs	
Systolic blood pressure (mmHg)	138.5 (123.0-156.0)
Heart rate (beats per minute)	88.5 (78.0-103.0)
Oxygen saturation (%)	98 (97.0-99.0)
Respiration rate (breaths per minute)	18 (16.0-20.0)
Temperature (°C)	36.9 (36.6-37.0)
Wells[18] score	
Wells score	1.5 (0.0-3.0)
PE likely (4.5 points or more) PE unlikely (4.0 points or less)	35 (17.7) 163 (82.3)
Adjust-Unlikely testing results	
PE the most likely diagnosis PE not the most likely diagnosis	23 (11.6) 175 (88.4)
D-dimer result (ng/ml FEU)	320 (199.0-737.5)
No pulmonary imaging required	143 (72.2)
Diagnosed with PE at index visit	7 (3.5)
Emergency department disposition	
Discharged home	161 (81.3)
Admitted to hospital	32 (16.2)
Transferred to another facility	3 (1.5)
Left prior to assessment completion	2 (1.0)

2.4.2 Primary Outcome

Table 2.2 displays the results. The recruitment rate averaged 9 patients per site, per week (SD 5.7) and the missed eligible rate averaged 6 patients per site, per week (SD 3.5). An average of 13 patients per week (SD 3.7) were recruited from the ED and 5 patients per week (SD 1.8) were recruited from the urgent care centre. The missed eligible rate averaged 8 patients per week (SD 2.3) in the ED and 3 patients per week (SD 2.1) in the urgent care centre. After 90 days, 2 patients withdrew and 191/198 (96.5%, 95% CI 92.9, 98.3%), had been contacted in follow-up.

Table 2.2 Feasibility results

Outcome	n % (95% CI) or Mean (±SD)
Recruitment and Missed Eligible Rates	
Recruitment rate (patients per site, per week)	9 (5.7) patients per site, per week
Emergency department	13 (3.7) patients per week
Urgent care	5 (1.8) patients per week
Missed eligible rate (patients per site, per week)	6 (3.5) patients per site, per week
Emergency department	8 (2.3) patients per week
Urgent care	3 (2.1) patients per week
Follow-up	
Withdrew	2/200 patients, 1% (0.3 – 3.5%)
90-day follow-up completed	191/198 patients, 96.5% (92.9 – 98.3%)
Completed via telephone	175/198 patients, 88.4% (83.2 – 92.1%)
Self-completed via email/text survey link	16/198 patients, 8.1% (5.0 – 12.7%)
Lost to follow-up	7/198 patients, 3.5% (1.7 – 7.1%)

2.4.3 Secondary Outcome

Figure 2.3 summarizes the diagnostic performance of the Adjust-Unlikely rule. Of the 143 patients with a negative Adjust-Unlikely rule on index visit, 1 patient out of 143 who had a negative Adjust-Unlikely test was diagnosed with PE during follow-up 0.7% (95% CI 0.1, 3.9%). Overall, 143/198 (72.2%, 95% CI 65.6, 78.0%) patients tested negative with Adjust-Unlikely.

The patient who was diagnosed with PE during follow-up was an 88-year-old man who initially presented to the ED with shortness of breath. The treating physician indicated that PE was not the most likely diagnosis and the patient's D-dimer result was 363 ng/ml FEU at the index visit. The patient was admitted with worsening dyspnea and congestive heart failure, with a background of severe aortic stenosis. The patient underwent a transcatheter aortic valve implantation procedure and was discharged from the hospital 11 days after ED presentation with no post-procedure complications. The patient returned with shortness of breath 18 days after their initial ED presentation. A CT pulmonary angiogram ordered on readmission revealed multiple PEs in the segmental pulmonary arteries in the right upper and middle lobes.

2.5 Discussion

To date, most diagnostic PE studies obtained in-person consent from patients at the point of testing. We assessed the feasibility of recruiting patients by telephone. We found that telephone recruitment is feasible because the average recruitment rate was 9 patients per site, per week, however, the missed eligible rate averaged 6 patients per site, per week, which is higher than our predefined feasibility threshold of no more than 2 patients per site, per week. Follow-up by telephone, text or email was successful in 96.5% of participants. The pilot results support our hypothesis that Adjust-Unlikely is safe and efficient for PE testing.

There is evidence to suggest that calling patients following ED discharge can be an effective and well-accepted method for study recruitment in other areas of emergency medicine research.[68,69,71] For example, in a prospective, multicentre evaluation of anticoagulated ED patients with blunt head trauma, Offerman and colleagues established successful contact with 501/506 eligible participants by telephone after ED discharge and they obtained consent for study inclusion in 500/501 of these cases.[68] Our recruitment rate averaged 9 patients per site, per week, and was approximately 3 times the recruitment rate of the YEARS study[23] which did not require informed consent. Our study took place at two centres staffed by the same 50 physicians. Higher adoption of Adjust-Unlikely compared to YEARS (conducted over 12 sites) may be one explanation. Another factor could be the country of study. European studies report a higher prevalence of PE among diagnostic studies compared to North American studies.[51] Higher prevalence could signal more selective and lower testing rates.

Our recruitment rate was approximately 5 times higher than that seen in the Canadian PEGeD study and 8-12 times higher than those seen in the ADJUST-PE and RELAX-PE studies[25,27]. The PEGeD study applied a hybrid approach to recruitment whereby recruitment took place prior to testing at some sites and by telephone at other sites. The ADJUST-PE[25] and RELAX-PE[27] studies were European studies conducted across Belgium, France and Switzerland, where in-person consent was required prior to PE testing. Additionally, the ADJUST-PE study included sites in the Netherlands, where in-person consent was not required, but the treating physician still informed patients about the study protocol and telephone follow-up.[25] A possible explanation for the lower recruitment rates observed in these studies is that large proportions of patients potentially eligible for participation were not identified by the researchers and/or the patient's treating physician testing for PE. In our study, the Adjust-Unlikely rule was implemented as the standard of care for all patients with suspected PE at both hospitals prior to the start of data collection. An advantage of recruiting patients by telephone after they left the ED was that it allowed us to identify and attempt to contact all patients eligible for participation.

In general, missed eligible rates have not previously been reported in diagnostic PE research, so it is difficult to compare our rate to other similar studies. Outside of PE research, other clinical decision rule validation studies in Canadian EDs have reported on the proportion of eligible patients who were not recruited. For example, in their 2005 multicentre prospective cohort study comparing the performance of the Canadian Head CT rule to the New Orleans Criteria, Stiell and colleagues reported that a total of 1541/4248 eligible patients were not recruited to the study.[88] The study was conducted over a two and a half year period across 9 sites, which works out to an average missed eligible rate of just over 1 patient per site, per week. More recently, Perry and colleagues reported that a total of 1829/9436 eligible patients were not recruited to their 2021 prospective validation study on the Canadian TIA score.[89] Conducted across 13 sites over a five year period, this works out to an average missed eligible rate of less than 1 patient per site, per week. These rates are considerably lower than our study's missed eligible rate averaging 6 patients per site, per week. However, the design of these studies differs from our study in that missed eligible patients were classified as patients with incomplete data forms or outcome assessments.[88,89] Neither of these studies required successful contact with, or informed consent from patients for study recruitment. At the time of telephone follow-up, enrolled patients had the opportunity to give consent.[88,89] Patients who could not be contacted were classified as lost to follow-up,[88,89] whereas in the present study, all patients with whom we could not get in contact with for the initial consent call were classified as missed eligible.

After 90 days, 96.5% of patients had been successfully contacted for follow-up. This rate is lower than the 90-day follow-up rate of recent PE testing studies such as PEGeD,[24] YEARS,[23] ADJUST-PE[25] and RELAX-PE,[27] all of which had follow-up rates greater than 98%. Both PEGeD[24] and the YEARS study[23] provided participants with an option to attend a scheduled outpatient appointment for follow-up. Researchers from the ADJUST-PE study also contacted family physicians,[25] both of which may have minimized loss to follow-up.

It is worth noting that 143 patients declined to participate in the present study and a total of 200 patients were included. In comparison, 136 people declined participation in the PEGeD study and 2017 were included,[24] 147 patients declined participation in the ADJUST-PE study and 3346 were included,[25] and 157 patients declined participation in the RELAX-PE study, where a total of

1507 patients were included.[27] It is possible that approaching patients at the time of testing reduces the proportion who decline participation. Contact by telephone may be perceived as more nuisance and annoying, making people less inclined towards study participation.

This study has several strengths. The treating physician documented whether or not PE was the most likely diagnosis in real-time, blind to the patient's D-dimer result. Venous thromboembolism testing in follow-up was independently adjudicated, blind to the patient's Adjust-Unlikely testing results at their index emergency visit. As for all PE testing follow-up studies, we relied on patients to tell us if they were tested for venous thromboembolism at another hospital. If a patient did not know that they were being tested for venous thromboembolism, we would not have these cases adjudicated. We did not capture whether physicians applied a screening decision rule such as the PERC rule[90] before testing for PE. Patients who were not tested with Adjust-Unlikely were excluded which could have introduced spectrum bias. Finally, as this was a prospective pilot study with a small sample size, our results cannot be used to determine the safety of the Adjust-Unlikely rule for diagnosing PE in emergency patients.

2.6 Conclusions

In this study, recruitment by telephone did not meet our predefined thresholds for feasibility. The recruitment rate was high, follow-up was feasible, but the high missed eligible rate suggests that telephone recruitment would miss too many eligible patients.

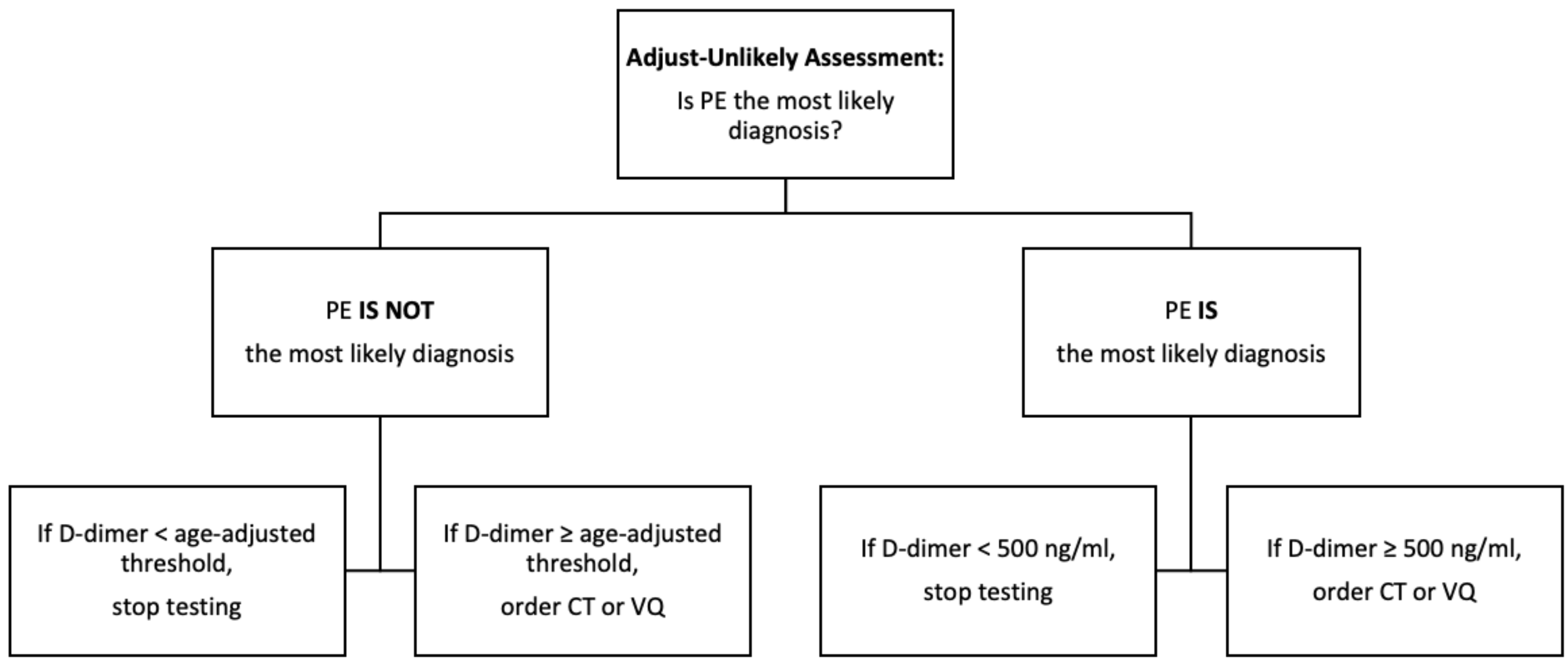


Figure 2.1 The Adjust-Unlikely decision rule

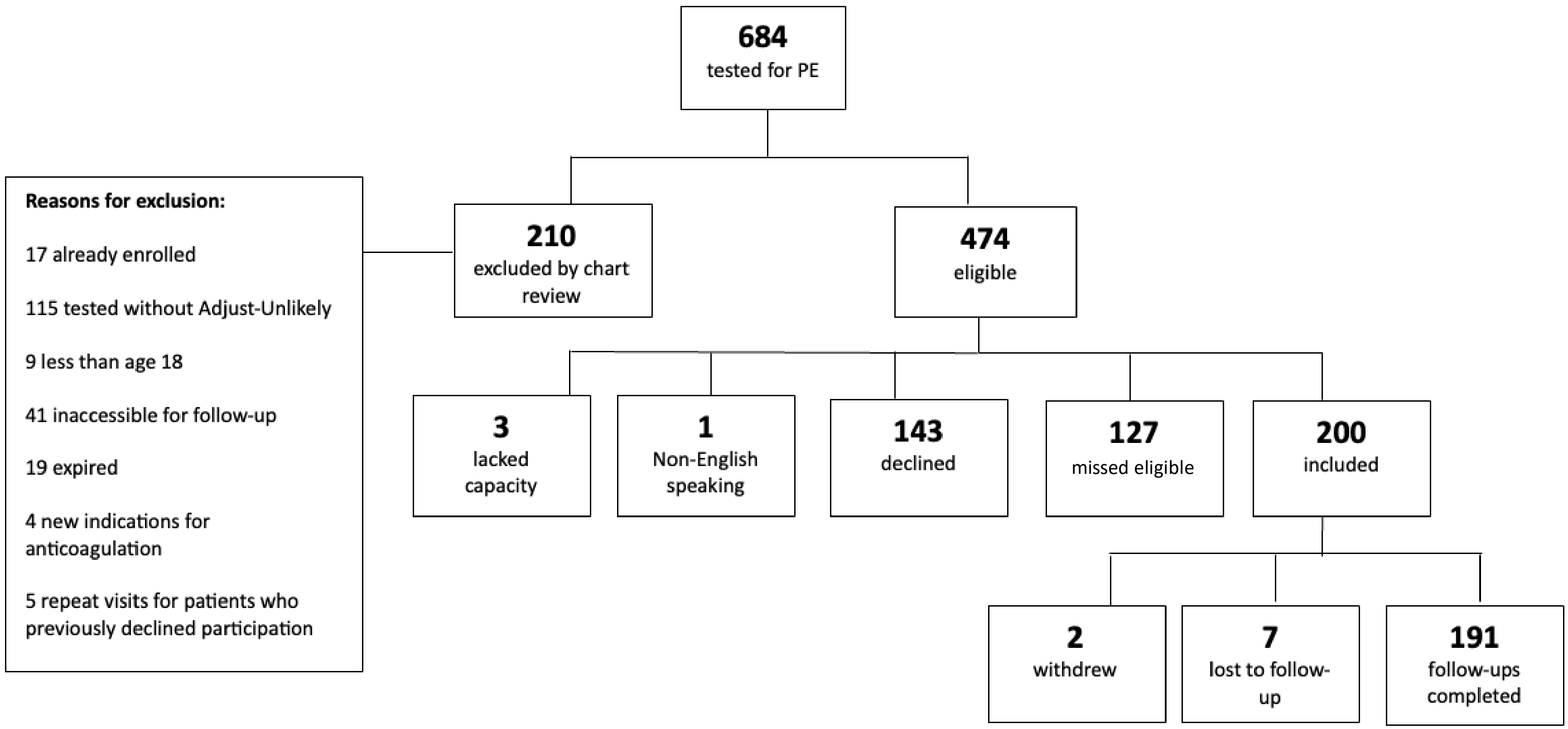


Figure 2.2 Flow diagram of study cohort

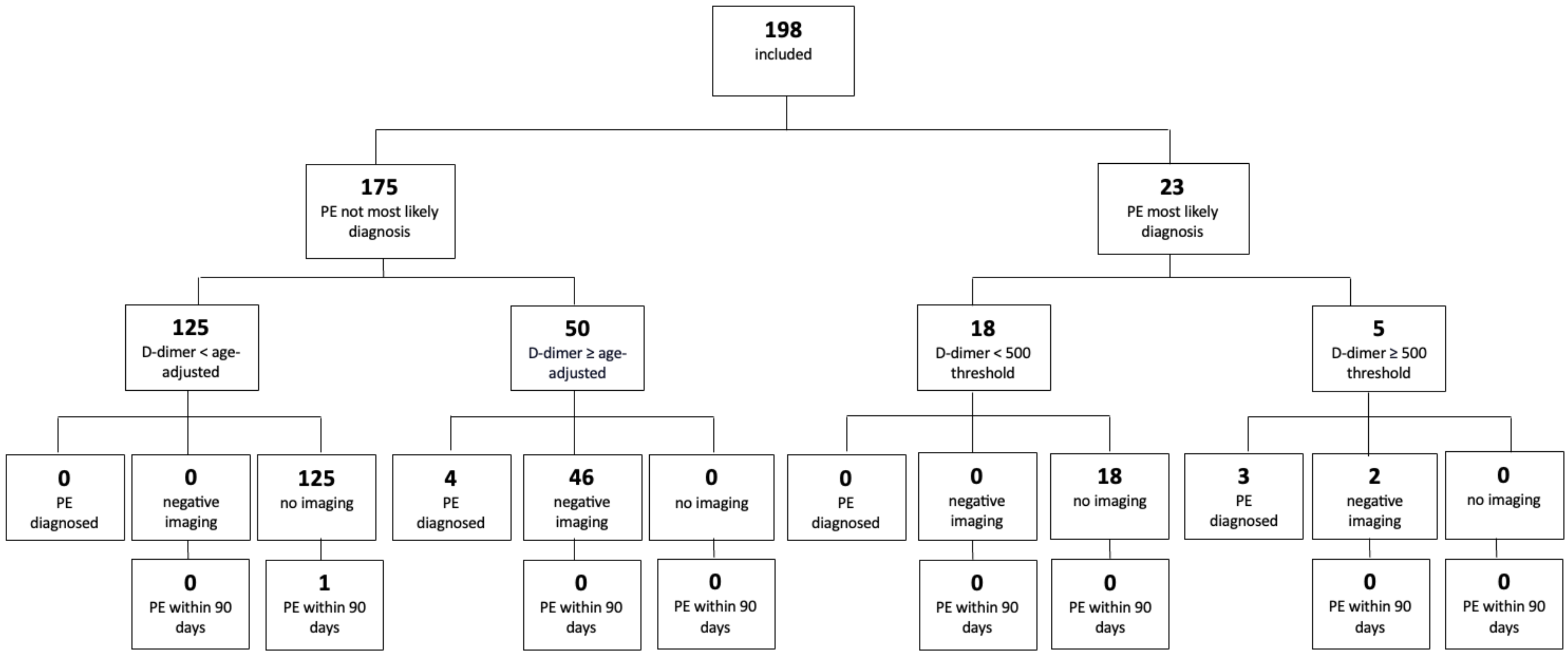


Figure 2.3 Diagnostic performance of the Adjust-Unlikely rule

Chapter 3: Spectrum bias associated with telephone recruitment of emergency patients with suspected pulmonary embolism

3.1 Abstract

Background: Prior studies on pulmonary embolism (PE) testing recruited in the emergency department (ED). In-person ED recruitment is challenging and it is unclear if alternative methods could affect the study population. This study assessed whether telephone recruitment of emergency patients tested for PE introduced spectrum bias.

Methods: This study used data from a prospective pilot study in one ED and one urgent care centre, in Ontario, Canada. Adult patients tested for PE using the Adjust-Unlikely decision rule were identified retrospectively and recruited by telephone. Patients who consented to participate were followed for 90 days to identify subsequent diagnoses of venous thromboembolism. We used multivariable logistic regression to compare the demographics (age, sex, D-dimer result, PE testing result, day of week and time of day) of included patients to missed eligible patients (those who could not be contacted by telephone) or patients who declined participation. We also compared included patients to excluded patients.

Results: 684 patients were tested for PE between March 24 and June 10, 2023. 200 patients were recruited, 210 were excluded, 127 were missed, 4 were unable to consent and 143 declined participation. The median age of included patients was 58, 72.2% were female and 3.5% were diagnosed with PE on index visit. Median D-dimer result was 320 ng/mL FEU, 49.5% were tested during daytime, 78.8% on a weekday. After adjusting for PE testing result, D-dimer, testing day of week and time of day, included patients were older (aOR=1.07, 95% CI=1.02–1.13) and more often female (aOR=1.59, 95% CI=1.06–2.37) compared to missed eligible patients and patients who declined participation. Included patients were younger (aOR=0.92, 95% CI=0.87–0.97) and more often female (aOR=1.95, 95% CI=1.27–2.98) compared to excluded patients.

Conclusions: We detected spectrum bias arising from telephone recruitment methods.

3.2 Introduction

Pulmonary embolism (PE) is difficult to diagnose because signs and symptoms are non-specific and overlap with many other serious conditions. At least eleven evidence-based PE decision rules have been developed to standardize testing practices and reduce unnecessary diagnostic imaging for patients.[12] Newer approaches that combine the use of a validated decision rule with D-dimer blood test results have demonstrated false negative rates of less than 2% and efficiencies between 40% and 66% when applied.[23-25,27]

There are a number of benefits to safely reducing unnecessary imaging in patients with suspected PE. However, the validity and generalizability of prior studies must be interpreted within the context of methodology limitations such as strict exclusion criteria, convenience sampling, and consenting patients for study participation in-person at the time of PE testing. Additionally, in past studies it was not standard practice to report the proportion of patients eligible for participation who were not included in the study population. It is unclear how the processes for eligibility screening and recruitment could introduce spectrum bias, which can occur when a study population does not reflect the all types of patients and presentations encountered in clinical practice.[72] The effect is potential misrepresentation of diagnostic test performance in everyday clinical practice.[72]

In their 2023 study, de Wit and colleagues found that only 56% of all ED patients tested for PE presented between the hours of 5pm and 8am.[54] However, it is not feasible to have research assistants recruiting emergency patients for study participation 24 hours a day. The severity of illness may be different for patients who present to the ED at night compared to during the day,[91] and for those presenting on a weekend versus a weekday.[92] Excluding patients who lack the capacity to consent such as those with delirium or dementia could also bias the study population towards younger participants. Given that D-dimer levels increase with age,[93] the efficiency of D-dimer observed in recent studies may be higher than what would be observed in the general population.

The ideal diagnostic management study population would mirror the population of all eligible patients as closely as possible.[72] However, recent studies have not reported on the characteristics of these patients or compared excluded patients to those who were recruited. The objective of this study was to compare the characteristics of patients recruited to our pilot feasibility study by telephone, to those missed eligible (defined as those eligible for participation who could not be contacted) or who declined participation, in order to determine if our methods introduced spectrum bias. We hypothesized that compared to missed eligible and patients who declined participation, recruited patients would be older.

3.3 Methods

This study was approved by Clinical Trials Ontario (Project ID 4269).

3.3.1 Study Setting and Population

We conducted a secondary analysis of data obtained from a prospective management pilot study in one ED and one urgent care centre, in Kingston, Ontario, Canada. The study aimed to assess the feasibility of recruiting patients tested for suspected PE in the ED using the 'Adjust-Unlikely' rule[54] by telephone after discharge, and following them clinically for 90 days. Patients were eligible for inclusion if their emergency physician tested them for PE. Patients less than 18 years of age, patients tested for PE without using the Adjust-Unlikely rule, patients whose D-dimer level was known before assessment of whether PE was the most likely diagnosis, patients who had a new indication for anticoagulation on assessment (other than PE), patients who were inaccessible for follow-up (defined as living in long-term care or nursing homes, incarcerated, unhoused and/or without a reliable telephone number in their medical record) or expired, patients who previously declined participation, and patients who had previously participated in the study were excluded.

3.3.2 Study Protocol

The Adjust-Unlikely rule combines the use of clinical judgement on whether or not PE is the most likely diagnosis with D-dimer testing results.[54] The age-adjusted D-dimer cut-off is used to exclude PE when it is not the most likely diagnosis in the opinion of the treating physician, and the standard manufacturer-recommended cut-off is used to exclude PE when it is the most likely diagnosis in the opinion of the treating physician. This protocol was introduced at the participating sites in December 2022 following a systematic educational campaign for all staff and resident physicians.

After ED, urgent care centre or hospital discharge, trained research assistants reviewed D-dimer blood tests, computed tomography (CT) pulmonary angiograms and ventilation-perfusion (VQ) scans ordered in the ED and urgent care centre to identify patients tested for suspected PE. A manual chart review was conducted to identify cases that met exclusion criteria. Eligible patients then received a maximum of three telephone calls (one during the weekday, weeknight, and weekend) to obtain verbal consent for study inclusion.

Research assistants extracted patient age, sex, and PE testing results at index visit from the medical record for all included patients, missed eligible, patients who declined participation and excluded patients. For all patients who had D-dimer testing, the D-dimer order time of day, day of week and result were also extracted from the medical record.

3.3.3 Key Outcome Measures

We were specifically interested in the selection bias which might be introduced by our telephone consenting process. For that reason, the primary analysis was a comparison of included patients to all other eligible patients who were not enrolled (those who declined participation or who were missed). The outcome of interest was group status (included versus missed/declined). The predictor of interest was age because we hypothesized that older patients would be more likely to answer and engage in a telephone conversation than younger patients. We included the following potential confounding variables: sex, PE testing results, D-dimer results, day of week, and time of day of testing. We were also concerned that emergency physicians might be selective in which patients they use Adjust-Unlikely testing. Our secondary analyses were a comparison of patients who were included to those who were excluded from the study specifically because Adjust-Unlikely was not followed, and a comparison of included patients to all excluded patients. The outcome of interest was group status (included versus excluded).

3.3.4 Data Analysis

A descriptive analysis was performed reporting statistics using measures of frequency and central tendency. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression to assess for spectrum bias among the included study patients. The independent variable of interest was age (unit of analysis 5 year). Covariables were sex, PE testing result (positive or negative for PE), testing day of week (weekday versus weekend), testing time of day (daytime, evening and night) and D-dimer result (unit of analysis 100 ng/ml FEU). Our primary analysis was a comparison of patients who were included to those who were eligible for inclusion but either were missed (defined as those who could not be reached) or else declined study participation (Model 1). Our secondary analyses were: Model 2, comparing included patients to excluded patients whose testing did not follow the Adjust-Unlikely decision rule. We obtained testing day and time from the D-dimer order and from ED registration time for excluded patients who did not have D-dimer testing. Model 3 compared included patients to all excluded patients. Models 2 and 3 did not adjust for D-dimer results.

Using the general rule of thumb, we estimated that a model containing 7 covariables would require 70-140 outcomes in the smallest outcome group. The pilot feasibility study recruited 200 patients. Two hundred and seventy patients were missed eligible/declined, 115 patients were excluded because their testing did not follow Adjust-Unlikely testing and 210 patients were excluded. Analysis was conducted using SPSS version 29.

3.4 Results

Between March 24, 2023 and June 10, 2023, 684 patients were tested for PE at both hospitals. A total of 210 patients were excluded, 19 because they died prior to receiving a telephone call (see Figure 3.1). From a total of 474 eligible patients, 200 were recruited, 143 declined participation and 127 were missed (could not be reached). Four patients were unable to give consent. Two patients who consented to study inclusion withdrew from the study during the follow-up period. Table 3.1 compares included, missed eligible/declined patients, those excluded specifically because their testing did not follow Adjust-Unlikely testing, and all excluded patients. Table 3.2 displays the results of the multivariable logistic regression models.

Table 3.1 Demographics of included, missed eligible/patients who declined participation and excluded patients

Description	**Number (%) or median (IQR)**			
Population	**Included patients**	**Missed eligible or patients who declined study participation**	**Excluded because Adjust-Unlikely not followed**	**All excluded patients**
Total n	198 (100)	270 (100)	115 (100)	210 (100)
Age (years)	58 (40.8–69.3)	52 (32.0–66.0)	68 (55.0–79.0)	68 (50.0–78.0)
Female	143 (72.2)	167 (61.9)	59 (51.3)	110 (52.4)
Testing time of day				
Day	98 (49.5)	145 (53.7)	69 (60.0)	117 (55.7)
Evening	62 (31.3)	81 (30.0)	34 (29.6)	63 (30.0)
Night	38 (19.2)	44 (16.3)	12 (10.4)	30 (14.3)
Testing day of week				
Weekday	156 (78.8)	218 (80.7)	95 (82.6)	164 (78.1)
Weekend	42 (21.2)	52 (19.3)	20 (17.4)	46 (21.9)
D-dimer result (ng/ml FEU)	320 (199.0–737.5)	350.5 (199.0–892.8)	581.5 (327.0–966.0)	537 (249.0–1145.8)
Diagnosed with PE at index presentation	7 (3.5)	10 (3.7)	5 (4.3)	9 (4.3)

Table 3.2 Multivariable logistic regression models

Variable	Adjusted odds ratio (95% CI)		
	Included compared to missed eligible / patients who declined participation (n=468)	**Included compared to excluded patients whose testing did not follow Adjust-Unlikely (n=313)**	**Included compared to all excluded patients (n=408)**
Age (unit of analysis 5 years)	1.07 (1.02 – 1.13)	0.86 (0.80 – 0.93)	0.92 (0.87 – 0.97)
Sex (reference male)	1.59 (1.06 – 2.37)	1.81 (1.09 – 3.01)	1.95 (1.27 – 2.98)
PE testing result (reference negative)	1.24 (0.40 – 3.83)	1.12 (0.32 – 3.90)	1.03 (0.36 – 2.96)
Day of week (reference weekday)	1.06 (0.67 – 1.69)	1.12 (0.60 – 2.11)	0.87 (0.53 – 1.42)
Tested in the evening (reference daytime)	1.13 (0.74 – 1.74)	1.23 (0.71 – 2.12)	1.11 (0.70 – 1.76)
Tested at night (reference daytime)	1.26 (0.76 – 2.10)	2.25 (1.06 – 4.79)	1.62 (0.92 – 2.88)
D-dimer result (unit of analysis 100 ng/ml FEU)	0.98 (0.96 – 1.01)		

Included patients were older than missed eligible patients / those who declined, and younger than excluded patients. Included patients were more likely to be female (aOR 1.59, 95% CI 1.06–2.37) than missed eligible patients and patients who declined participation. Included patients were also more likely to be female than patients excluded because Adjust-Unlikely was not followed and all excluded patients. A sensitivity analysis comparing included patients to excluded patients which included D-dimer testing (n=360 patients) found an aOR of 0.94 (0.89–1.00) for age and 1.70 (1.08–2.69) for female patients.

No included patients died during the 90-day follow-up period.

3.5 Discussion

In this study, we found evidence of spectrum bias in our study population. The included study population was older than those who fulfilled eligibility but were missed or else declined study participation. The included population was younger than those who were excluded from study participation. Female patients were overrepresented in our study population compared to patients who were eligible but not included as well as patients who were excluded from study participation.

Previous research has demonstrated age-based[94,95] and sex-based differences[96] in PE testing practices in the ED. For example, in 2017, Buchanan and colleagues found that age was associated with further PE testing in PERC negative patients.[95] A retrospective cohort study conducted in two EDs in the United States also found that patient sex influenced the odds of receiving care consistent with the revised Geneva score[20] guidelines, with males found to be less likely than females to receive guideline-consistent ED care.[96]

Several studies have shown that females are more likely than males to participate in research.[97-100] For example, in a telephone survey of factors affecting the Australian general public's participation in health research surveys, Glass and colleagues found that females were more willing to participate than males.[97] A study on factors associated with young employee participation in an online, mailed or telephone health survey in Finland found that non-respondents were more often males than females.[98] Similarly, in Norway, researchers contacted a random sample of non-respondents to their mailed respiratory health questionnaire by telephone to identify potential causes of non-response.[99] They found that females had a significantly higher response rate than males.[99] Additionally, like our results, these studies also found that younger people were more likely to decline participation[97] or else not respond.[98,99]

To our knowledge, only one previous diagnostic PE study from 2001 reported on the characteristics of excluded patients and compared them to those who were included in the study population.[101] Researchers found that there were no statistically significant differences in age or sex between the groups, but that excluded patients were statistically significantly more likely to be hospitalized and have non-diagnostic VQ scans than included patients.[101] Additionally, researchers found that compared to included patients, those excluded specifically because they declined participation or were unable to give consent were older and more likely to have a malignancy.[101] Although we did not collect data on malignancy, we noted that 19/210 (9%) of excluded patients died before they could be reached by telephone to offer study participation, suggesting telephone recruitment led to exclusion of patients with severe illness.

The ED is an increasingly demanding environment where recruiting patients to research presents unique challenges. The characteristics of patients who were not successfully recruited to recent diagnostic PE studies has not been reported, so it is difficult to compare the spectrum bias detected in the present study to other similar studies. In general, future studies could benefit from a more targeted strategy to increase the recruitment of males and patients from a variety of age groups. As for all PE testing studies, the study population was limited to those tested according to the decision rule pathway under investigation. Although it is impractical to remove exclusion criteria entirely, widening the criteria such that not all patients tested for suspected PE without the intended pathway are excluded could help mitigate potential spectrum bias. Additionally, an assessment of spectrum bias should be a standard for reporting on PE diagnostic research. The lack of reporting in previous studies may help to explain why some decision rules are found not to perform as well as they do in their original validation studies. For example, in an individual patient data meta-analysis, the YEARS and PeGED algorithms were found to have false negative rates higher than what was originally reported.[12]

In the rise of evidence-based medicine, clinicians must be able to recognize how the patients and presentations they encounter may be different from the populations studied in research.[102] Emergency physicians have reported a lack of trust in validated decision rules for PE testing.[6] It is possible that clear reporting of the characteristics of non-recruited patients would increase the validity of results and help clinicians to feel more comfortable and confident incorporating them into their clinical practice in the future.

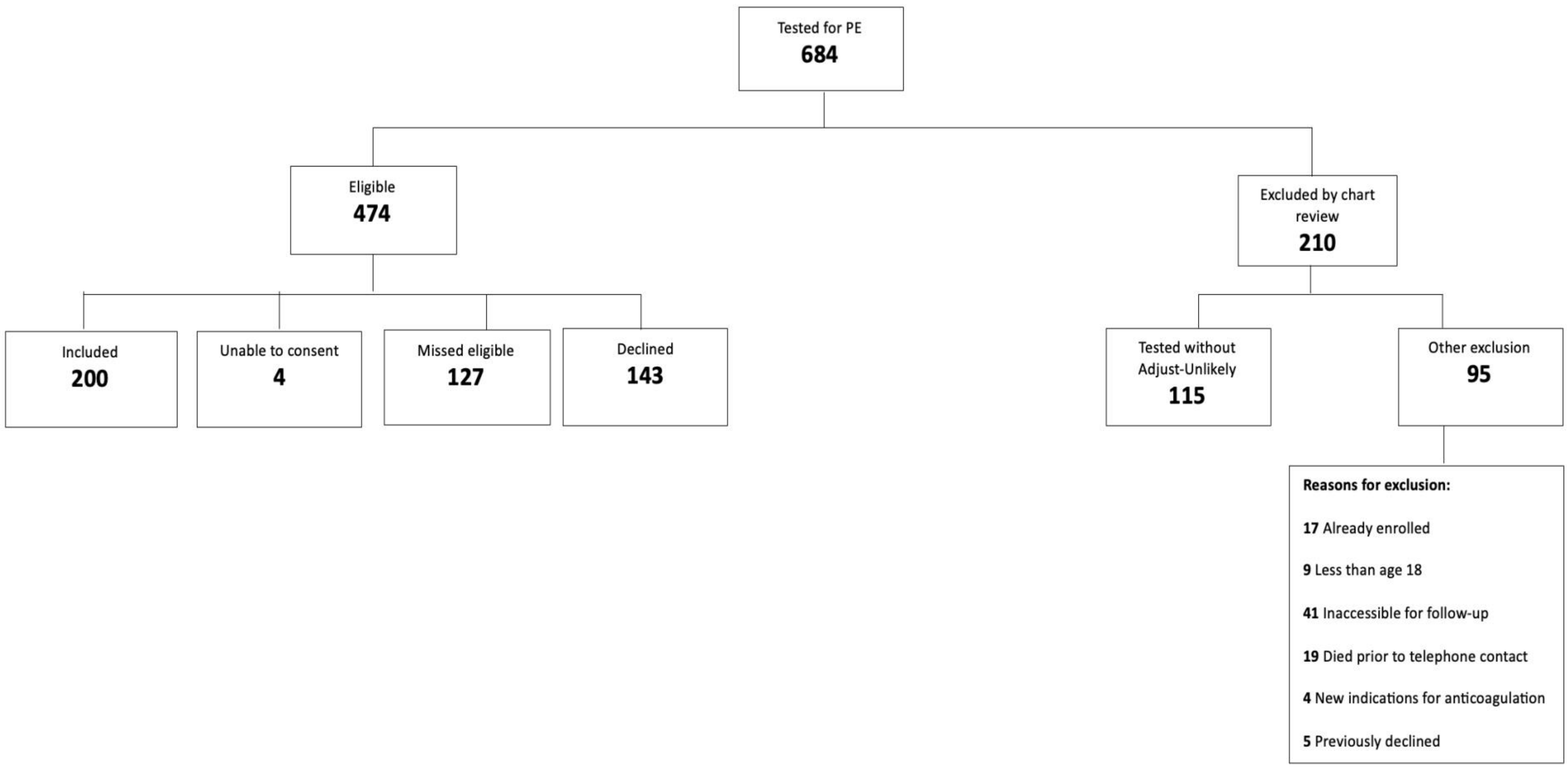
3.6 Limitations

The current study used data from a prospective pilot study with a small sample size, which limits the interpretation of the multivariable logistic regression analyses. The study was conducted in two hospitals in a single Canadian city and our findings may not be generalizable to other populations. The future full study will report the false negative rate of Adjust-Unlikely more precisely. We did not follow missed eligible, those who declined and those who were excluded for 90 days, therefore we don't know whether the spectrum bias we detected had any effect on the reported 90-day false negative rate for Adjust-Unlikely PE testing.

3.7 Conclusions

We detected spectrum bias associated with telephone recruitment methods. Future PE diagnostic research should report on the characteristics of missed eligible, declined and excluded patients and increase efforts to recruit male participants and participants from a variety of age groups.

Figure 3.1 Flow diagram of included patients



Chapter 4: General Discussion

4.1 Summary of Findings

To address a gap in evidence-based ED PE testing, our research group previously derived a new clinical decision rule for PE testing.[54] In the present studies, we established that telephone recruitment of patients to a full study prospectively assessing the safety and efficiency of the Adjust-Unlikely rule did not meet the predefined thresholds we set for feasibility. We observed an average recruitment rate of 9 patients per site, per week and an overall follow-up rate of 96.5%, both of which exceed the predefined feasibility thresholds. However, more eligible patients were missed than outlined in the predefined threshold, an average of 6 patients per site, per week. We also found that almost a third of all patients eligible for participation declined. Finally, we detected spectrum bias in our study population. After adjusting for age, sex, PE testing result, D-dimer, testing day of week and time of day, we found that included patients were older than missed eligible patients and those who declined, and younger than excluded patients. Included patients were also more likely to be female compared to both groups.

4.2 Research Implications

Our findings raise important questions about previous recent PE diagnostic studies,[23-25,27] where recruitment rates were 3-12 times slower. It is possible that the emergency physician adoption rate of Adjust-Unlikely was higher than in other clinical decision rules in previous studies. Prior to the start of the study, Adjust-Unlikely was implemented as the standard of care for all emergency patients tested for suspected PE in the ED and urgent care centre. The rule was designed to be easy and attractive to apply. By integrating the algorithm directly into the electronic medical record at the point of D-dimer testing, adoption did not impede clinical workflow. Consenting patients after they left the ED also allowed us to identify and attempt to contact all patients eligible for participation. The disparity in recruitment rates observed between our study and prior studies raises the question of whether in-person convenience sampling has driven prior PE testing research, raising the question of whether the patients included in prior studies were truly representative of all ED patients tested for PE. Future studies, at least in Canada, should expect to recruit at a rate which is higher than those reported in prior PE testing studies.

While the follow-up rate was high, it was not as high as previously reported studies.[23-25,27] Achieving an overall follow-up rate near 100% is especially important when the expected false negative rate is less than 2%. There is a vast difference in the interpretation of safety with a 1% false negative rate, if, for example, 5% of patients are lost to follow-up. In the full study, if many of the patients lost to follow-up are diagnosed with venous thromboembolism during the 90-day follow-up period, the Adjust-Unlikely rule would appear safer to apply in research than it would be to apply in clinical practice. Other studies used a combination of medical record review, telephone calls, clinic visits, and contact with the family physician. However, the exact methods of follow-up were not described comprehensively and a breakdown of methods by patient numbers has not previously been provided. Details such as how family physicians were contacted, how many follow-up call attempts were made per patient, and details surrounding the clinic appointments (such as whether they were scheduled during the participant's index visit or after ED discharge, whether they were part of the standard of care or study-specific, etc.) are unclear. Future research should clearly report on methods of follow-up to allow critical appraisal of the follow-up methods (ensuring they were the best they could be) and to ensure the methods are reproducible.

Despite exceeding the predefined feasibility thresholds for recruitment and follow-up, we were unable to contact a high proportion of eligible patients at each site, each week, which introduced spectrum bias in our study population. This raises the question of whether the diagnostic performance of previous PE decision rules was also misrepresented by methodology limitations. For example, if research assistants were only available to recruit patients in-person during the daytime, the safety and efficiency of previously validated clinical decision rules may have been biased towards patients with more severe presentations.[91] It is possible that the false negative rate would be higher and efficiency would be lower across the proportion of patients tested for suspected PE overnight.

Past PE studies have not reported on missed eligible patients. Reporting on missed eligible patients and comparing their characteristics to those of the study population should be the new standard practice for PE diagnostic research conducted in the ED. It is already a reporting standard in other types of ED decision rule validation studies. For example, studies on the Canadian Head CT rule,[88] Ottawa Ankle rules,[103] Ottawa Knee Rule,[104] Canadian C-Spine rule[105] and Canadian TIA score[89] all reported on the proportion of missed eligible patients who were not enrolled and compared their demographics and clinical characteristics to study participants. Our results support future PE testing studies reporting on missed eligible patient numbers, age and sex. International guidelines for venous thromboembolism research should take this into account in the future, and high-impact journals should require reporting on these items for publication. Doing so will also better equip physicians to apply the results of research to their own clinical populations.

As for the full study, our findings suggest that if we were to scale up using the pilot study's design, the diagnostic performance of the Adjust-Unlikely rule may be biased towards female patients. The effect is the potential misrepresentation of the Adjust-Unlikely rule safety and efficiency for male patients in the full study. Diagnostic performance in the full study could also be misrepresented by the statistically significant differences observed in age when we compared included patients to missed eligible, declined, and excluded patients. For example, we found that included patients were younger than excluded patients. Given that D-dimer levels increase with age,[93] the efficiency reported for the Adjust-Unlikely rule for the study population may have been higher than what would be observed for the population of excluded patients. The ideal study population should not be significantly different from the population of patients who are not included.[72] Thus, the full study should be designed with the intent to reduce the proportion of missed eligible patients and recruit more males and participants of all ages.

Additionally, over half of all excluded patients in the pilot study were excluded because the treating physician deviated from the Adjust-Unlikely testing pathway. This includes patients who had a scan despite a negative D-dimer, who did not have a scan despite a positive D-dimer, and those who did not have a D-dimer at all. It appears that sometimes physicians 'cherry-pick' when and when not to follow the Adjust-Unlikely rule for testing patients with suspected PE. Removing deviation from the pathway from the list of predefined exclusion criteria could also help to reduce spectrum bias in the full study. In the full study, eligibility could be expanded to all patients who are tested for suspected PE in the ED, as long as their treating physician still documents whether they believe PE is the most likely diagnosis and order a D-dimer test. In addition to adjudicating all cases of venous thromboembolism testing performed in follow-up, index cases where the treating physician deviates from the Adjust-Unlikely testing pathway (defined as ordering imaging for their patient despite a negative Adjust-Unlikely rule) could also be adjudicated to assess for false negative results at baseline. Including these cases will also allow us to determine the proportion of all PE testing which adheres to the Adjust-Unlikely rule and perform logistic regression analyses to identify determinants of physician deviation.

Finally, to identify all episodes of venous thromboembolism testing during the follow-up period, patients had to report any testing outside of Kingston during the follow-up interview. While this is the gold standard method of follow-up for PE diagnostic research, it has limitations. It is possible that patients would be unaware when and if they are being tested for venous thromboembolism elsewhere, which could lead to underestimation of the false negative rate in the full study.

4.3 Future Directions

This work has informed the design and planning of our locally led, CIHR funded full study, the 'Emergency Medicine Pulmonary Embolism Testing Study (EMPET)', which will prospectively evaluate the safety and efficiency of the Adjust-Unlikely rule at eight ED sites across Ontario. The Adjust-Unlikely rule will be the standard of care for PE testing at all participating sites, but unlike the pilot study, patients will not be excluded if the treating physician deviates from the Adjust-Unlikely testing pathway. EMPET has received ethics approval for a waiver of informed consent. All patients deemed eligible for participation will be recruited to the study, which will reduce spectrum bias. All patients tested for PE with D-dimer will be included, whether their physician deviated from Adjust-Unlikely or not. Baseline and follow-up data will be collected by medical record review. Additionally, to check for venous thromboembolism diagnoses outside the local hospital, data from the Institute for Evaluative

Clinical Sciences (ICES) will be used. ICES captures reliable, province-wide data on health service use,[106] and will allow for more precise reporting on the false negative rate of the Adjust-Unlikely rule.

4.4 Translational Impact

Emergency patients want rapid progression through testing, personalized assessment and a confident diagnosis from their treating physician.[107] Existing evidence-based decision rules are complicated to apply and contribute to PE testing distress among emergency physicians.[6] The Adjust-Unlikely decision rule is the only PE testing rule that considers patient values and expectations, and physician preferences for clinical gestalt. If the EMPET study prospectively validates that Adjust-Unlikely PE testing is safe and efficient for emergency patients, it could be adopted by EDs across Canada and lead to more standardized practice and reduce potentially unnecessary CT pulmonary angiograms for patients. Limiting diagnostic imaging can help to reduce false positive[12] and nonsignificant incidental findings,[13] shorten ED visits[14] improve overcrowding, and ensure emergency imaging is available for patients who most need it.

4.5 Conclusions

The Adjust-Unlikely rule for PE testing was designed specifically to align with the demands of the ED environment, emergency physician preferences, and emergency patient values and expectations. We assessed the feasibility of a study protocol consenting emergency patients tested with the Adjust-Unlikely rule and following them clinically after they left the ED. The studies presented in this thesis demonstrate that contacting patients by telephone did not meet the predefined thresholds we set for feasibility. The missed eligible rate was high and we found evidence of spectrum bias in our study population. These results have important implications both locally, and for the broader venous thromboembolism research community. We have modified the design of our full study such that the requirement for informed consent is waived and data is collected solely through medical record review. With respect to PE diagnostic research, new standards for reporting are needed. Future studies should report on the missed eligible rate and include a formal assessment of spectrum bias.

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Appendix 1: Ethics Approval

Date: 22 February 2023

To: Dr Kerstin de Wit, Queen's University

CTO Project ID: 4269

Study Title: A pilot study to assess feasibility of evaluating the safety and efficiency of a simplified diagnostic approach for pulmonary embolism

Sponsor Study ID: N/A

Application Type: Observational Provincial Initial Application

Review Type: Delegated

Date Approval Issued: 22/Feb/2023

Study Approval Expiry Date: 22/Feb/2024

Dear Provincial Applicant,

Thank you for submitting the above referenced study on behalf of all Ontario centres through the Clinical Trials Ontario Streamlined Research Ethics Review System. The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board has reviewed the study and granted initial provincial approval as of the date noted above.

Provincial documents approved:

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Telephone Follow-up_v1_2022-12-02	02/Dec/2022	1
Adjust-Unlikely PE_Verbal Consent Log_v1_2022-12-02	02/Dec/2022	1
Adjust-Unlikely PE_Protocol_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Patient Information Sheet_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Data Extraction Form_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Telephone Consent_v1_2023-02-17	17/Feb/2023	1

Provincial documents acknowledged:

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Budget_v1_2023-02-03	03/Feb/2023	1

Note: Provincial REB approval does not confer ethics approval for participating centres. Each participating centre, including that of the Provincial Applicant, must submit the "Centre Initial Application" and receive approval from this REB prior to the conduct of the study at that centre. All other

required institutional approvals must also be obtained prior to the conduct of the study.

No deviations from, or changes to, the protocol should be initiated without prior written approval from Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial (such as a change in telephone number).

REB members involved in the research project do not participate in the review, discussion or decision.

Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Dean A. Tripp, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB)
Professor, Dept of Psychology, Anesthesiology & Urology
Queen's University
Kingston, ON K7L 3N6
HSREB@queensu.ca

Date: 23 March 2023

To: Dr. Kerstin de Wit, Kingston Health Sciences Centre

CTO Project ID: 4269

Study Title: A pilot study to assess feasibility of evaluating the safety and efficiency of a simplified diagnostic approach for pulmonary embolism

Sponsor Study ID: N/A

Application Type: Observational Centre Initial Application

Review Type: Delegated

Date Approval Issued: 23/Mar/2023

Study Approval Expiry Date: 22/Feb/2024

Dear Principal Investigator,

The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board has reviewed the application and granted approval for your centre to participate in this study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study at this centre.

Provincial Documents approved:

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Telephone Follow-up_v1_2022-12-02	02/Dec/2022	1
Adjust-Unlikely PE_Verbal Consent Log_v1_2022-12-02	02/Dec/2022	1
Adjust-Unlikely PE_Protocol_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Patient Information Sheet_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Data Extraction Form_v1_2023-02-03	03/Feb/2023	1
Adjust-Unlikely PE_Telephone Consent_v1_2023-02-17	17/Feb/2023	1

Provincial Documents acknowledged:

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Budget_v1_2023-02-03	03/Feb/2023	1

Centre Documents approved:

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Telephone Consent_v1_2023-03-15	15/Mar/2023	1
Adjust-Unlikely PE_Patient Information Sheet_v1_2023-03-15	15/Mar/2023	1
Adjust-Unlikely PE_Telephone Follow-up_v1_2023-03-15	15/Mar/2023	1

Document Name	Document Date	Document Version
Adjust-Unlikely PE_Master Linking Log_v1_2023-03-15	15/Mar/2023	1
Adjust-Unlikely PE_Data Extraction Form_v1_2023-03-15	15/Mar/2023	1

No deviations from, or changes to the protocol should be initiated without prior written approval of an appropriate amendment from Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Dean A. Tripp, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB)
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