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Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism: A Health Technology Assessment — Project Protocol

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RATIONALE AND POLICY ISSUES

Clinical Presentation

Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease, after myocardial infarction and stroke.[1] It occurs when a blood clot dislodges from a vein, travels through the venous system, and lodges in the blood vessels of the lung.[2] Blockages of the pulmonary artery and its branches can lead to obstruction of blood flow to the heart. Resultant pressure in the lungs may increase right heart pressure, causing right ventricular strain, which can lead to cardiovascular compromise and hypoxemia.[3] Other complications include pulmonary hemorrhage and infarct. PE is a major cause of emergency hospitalization, with clinical expression ranging from asymptomatic disease to sudden death. Acute PE can lead to chronic pulmonary hypertension, post-thrombotic syndrome, and right ventricular failure if it is not promptly diagnosed and treated.[4] Further, untreated PE can be fatal in up to 30% of patients. If administered quickly, anticoagulation therapy is highly effective at preventing extension of thrombus and can prevent mortality and morbidity associated with PE.[5]

PE is part of the continuum of venous thromboembolism (VTE), which also includes deep vein thrombosis (DVT).[6] Most PEs originate from thrombi in the leg or pelvic veins that have dislodged. Evidence of lower-limb DVT is found in about 70% of

patients who have sustained a PE.[1] However, asymptomatic PE can also present in patients without DVT.[7,8]

Assuming the incidence rate in Canada is similar to that in the United States (US), PE likely afflicts between 0.1% and 1% of the population.[9] An accurate estimate of PE incidence is difficult to obtain, because a large proportion of pulmonary emboli are detected on autopsy,[10] and not all of these cases are clinically relevant. About 80% of patients identified with PE at autopsy are unsuspected or undiagnosed before death.[9]

There are many challenges associated with diagnosing PE, one being the non-specific nature of common PE symptoms. The most common symptoms include dyspnea and chest pain.[11,12] The underlying cause of PE-related symptoms could be a plethora of alternative conditions, including rib or vertebral body fracture, acute myocardial infarction, pulmonary edema, pneumonia, neoplasm, or interstitial lung disease. Approximately 30% of patients with PE may be asymptomatic.[13] Unspecific patient symptoms can potentially lead to over-testing, as PE may be considered in the differential diagnoses of a range of symptoms.

PE rarely occurs in the absence of risk factors and the likelihood of occurrence increases progressively where multiple risk factors are present. Factors associated with the development of PE can be inherited or acquired. They include, but are not limited to, malignancies, immobilization, surgery, extremity paresis, hormone replacement therapy and oral contraception, and factor V Leiden mutation or other acquired thrombophilia conditions.[14] Patients who have DVT or who are taking medications that alter coagulation of the blood are also at risk of developing PE.[8,15] In addition, pregnant women are four to five times more likely to develop VTE, which is one of the leading causes of maternal death during childbirth.[16] However, a proportion of patients who develop PE may have no risk factors.

Risk Stratification

The likelihood of PE can be estimated using various risk stratification approaches (see Table 1; Appendix 5). A patient may initially undergo assessment with a clinical prediction rule or clinical gestalt. Patients with high probability of PE may proceed directly to imaging, while patients with low probability may undergo further testing such as Pulmonary Embolism Rule-Out Criteria (PERC) or D-dimer testing to further assess the need for diagnostic imaging. This may be supplemented by additional biochemical or imaging studies to rule out differential diagnoses or strengthen estimates of PE risk.

Evidence supports the practice of determining the clinical pretest probability of PE before proceeding with diagnostic testing.[17] The American College of Physicians (ACP) has provided best practice advice on the evaluation of patients with suspected acute PE, noting that the first step when evaluating a patient is to establish his or her pretest probability of PE.[18] Clinical prediction rules (also called clinical decision rules) aim to determine risk profile and the necessity of undergoing diagnostic testing. The ACP recommends using either the Wells or Geneva clinical prediction rules.[18]

The Wells rule combines seven items based on both objective criteria from patient history or physical examination, and physician judgment, into a total score.[19] Typically patients with scores lower than 4 are deemed low risk for PE, although there is variation in the cut-offs applied. The Geneva score differs from Wells in that additional diagnostic testing (electrocardiography, and/or chest radiography, and arterial blood gas) contributes to the score as well as consideration of risk factors and clinical presentation.[19] A revised Geneva score has been developed that can be determined independently of the additional diagnostic tests.

There is controversy regarding which rules are the most accurate for predicting acute PE,[20] but the Wells and Geneva rules have received the most extensive validation in the widest range of settings.[20,21] There is some evidence from systematic reviews (SRs) to suggest that the Wells rule is more accurate than the Geneva rule, but that the most appropriate tool may depend on the setting (i.e., low prevalence versus high prevalence [referred population]).[20,22] Adherence to protocols incorporating the Wells score and D-dimer testing has been demonstrated to result in a 20% to 30% reduction in the number of computed tomography (CT) examinations performed.[23] D-dimer is one of several lab-based or imaging studies that are not used to diagnose PE, but may be used to increase confidence in the decision to forego testing or rule out differential diagnoses. A negative D-dimer test in a low-probability patient can support the decision to forego additional diagnostic investigation. In addition to D-dimer, other tests include lower-limb compression ultrasound, echocardiography (transthoracic or transesophageal), chest X-ray, capnography, and electrocardiography. These modalities are used for rule-out of PE or prognostic assessment of confirmed PE. PERC is an additional tool that can be applied in patients with low pretest probability following initial clinical assessment to help assess whether D-dimer testing can be deferred.[24] It is based on parameters that are available at initial emergency department assessment and uses an eight-factor decision rule. The clinician must answer “no” to all questions for a negative result, which can rule out PE and defers the need for further testing.

Given that symptoms of PE are not specific, clinical features alone cannot confidently rule PE in or out and they are rarely used in isolation.[11] There is also a risk of false-negatives, which can result in patients not receiving further diagnostic testing or necessary treatment. The positive predictive value of risk stratification strategies, particularly clinical prediction rules, may be influenced to some extent by the prevalence of disease in the population, as well as cut-off values used.[22] Nevertheless, these scores may improve the efficiency of PE assessment and diagnostic yield of imaging studies,[21] and decrease the volume of

unnecessary imaging studies. Their use is in line with initiatives by Choosing Wisely and society partners, which recommend that clinicians avoid CT angiography in patients who are stratified at low risk of PE and receive either a negative PERC score or D-dimer measurement.[25]

Diagnostic Imaging

Patients who are deemed at high risk of PE following pre-imaging risk stratification, or based on unstable presentation, usually undergo diagnostic testing for confirmation of disease positivity (see Table 1; Appendix 5). Conventional pulmonary angiography (PA) has been previously regarded as the gold standard, but due to the requirement for right heart catheterization and insufficient sensitivity, it has been overtaken by alternative modalities.[26,27] Other less-invasive methods of diagnosing PE include computed tomography pulmonary angiography (CTPA), magnetic resonance pulmonary angiography (MRPA), ventilation-perfusion (V/Q) scanning planar scintigraphy, V/Q single-photon emission computed tomography (SPECT), or V/Q SPECT-CT, positron emission tomography–CT (PET-CT) and thoracic ultrasound**.** Each of these imaging modalities has strengths and limitations, and the appropriate modality may depend on the available expertise of health care providers and technology, whether adherence to acquisition protocols are followed, and whether specific patient risk factors (e.g., allergy to contrast dye) and clinical conditions (e.g., pregnancy) are present.[1] Not all modalities are widely available or in routine clinical use in Canada and other developed countries. This may be due to lack of availability or expertise, or practical considerations such as increased time required and complexity of performing the exam.[28]

CT overtook V/Q scintigraphy as the most frequently used imaging modality to diagnose PE in 2001.[29] Although CT is widely considered to be a more definitive test, a large multi-centre study reported that both CT and V/Q imaging used in conjunction with clinical probability assessment, D-dimer, and lower-limb ultrasound testing resulted in similar low rates of VTE events during three-month follow-up.[30] Because CT is associated with exposure to ionizing radiation and iodinated contrast agents (with the associated risk of malignancy and contrast allergy), there is concern about its overuse.[31] A surge in CT use and improvements in technology have led to an observed escalation in the diagnosis of PE (including sub-segmental PEs of unclear clinical importance),[29,30] but there is no evidence linking its increased use with improved patient outcomes.[32-34] Major technical advances in CT technology have led to the use of CTPA combined with indirect CT venography, electrocardiogram (ECG)-gated CTPA, and dual source/dual energy CTPA.[35] However, in patients with known allergy to contrast media, those with severe renal failure, and pregnant women, alternative imaging modalities are often considered, especially in the emergency setting.[4]

Policy Issues

Of the total population of patients who are evaluated for suspected PE, few are confirmed to have the condition, indicating a low diagnostic yield of current evaluation methods.[22,36] Studies report a range of values for the diagnostic yield of CTPA, ranging from less than 5% to 30%, depending on the clinical characteristics of the patient pool, and use of risk stratification strategies.[37-40] False-positive test results, which, depending on pretest probability,[41] can occur in approximately 10% to 42% of patients[42] who undergo CT scanning, can lead to unnecessary anticoagulation therapy, which carries substantial risk of adverse effects including hemorrhage (occasionally devastating or fatal), interactions with other medications, inconvenience in terms of attendance for repeated blood tests (possibly requiring time off work), implications for future dental and medical procedures, and costs (both to the patient and society).[43] False-negative CT results, which also occur at high frequency (e.g., 1% to 11%),[44] can lead to bypass of necessary treatment, complications, and death. The uncertain benefit of increased testing and the significant expense of PE could suggest that current CT utilization patterns for the diagnosis of PE are not cost-effective.[18] This is reflected in the increased diagnosis of mild PEs, which, if treated, may increase costs and possible harms, and may not reduce mortality. In light of these concerns, it is important to assess whether there are other cost-effective and safe alternatives.

The optimal diagnostic strategy for suspected PE among experts remains controversial,[46,47] and it can differ based on factors related to the health care setting (i.e., urban, rural, or remote) that may impact access to imaging. The optimal diagnostic strategy would, in theory, be one that has high diagnostic accuracy and clinical utility, at an acceptable cost. However, issues of access may also influence what is considered optimal for different populations. For instance, provision of timely diagnosis may be less feasible in rural and remote facilities due to lack of access to certain testing and imaging modalities and specialist expertise, as well as geographical barriers to care. Inability to access optimal diagnostic testing in a timely manner could increase the risk for missed diagnoses, as well as unnecessary anticoagulation due to either false-positives or long wait times to receive assessment.[9] Patient safety concerns associated with exposure to radiation and contrast media that accompanies several imaging studies also disproportionately affect specific patient groups, including pregnant women, and young women for whom the risk of breast cancer associated with radiation is higher.[9]

Summary and Project Goals

Patients with suspected PE should be assessed using appropriate diagnostic tests in a timely manner.[2,45] Timing of access to diagnostic test results may have a significant impact on the management of the condition and the effective use of health care resources.[9] The heterogeneous clinical presentation of PE and lack of specific symptoms can lead to myriad problems. These include the wide application of testing, which can be very costly and may result in over-diagnosis, false-positives, and unnecessary treatment. Although guidelines for PE diagnosis recommend the use of imaging tests,[12] the optimal diagnostic strategy for suspected PE remains uncertain,[46,47] and it may vary depending on the health care setting due to access to the technology. Thus, the goal of this health technology assessment (HTA) is to conduct an assessment of the evidence to inform formulation of recommendations regarding the optimal diagnostic strategy, including risk stratification, for acute PE in the current context of care, considering benefits, harms, and costs, as well as patient experiences, implementation issues, and environmental impacts.

POLICY QUESTION

What is the optimal diagnostic strategy for acute PE in urban, rural, and remote settings? (Note: For the purposes of this report, urban, rural and remote settings will be discussed in the context of availability of testing modalities, geographical barriers and other accessibility concerns, and types of institutions [i.e., primary care to tertiary care].)

OBJECTIVES

The objective of this HTA is to address the policy question through an assessment of the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patient experiences and perspectives, implementation issues, and environmental impacts of strategies for the diagnosis of adults with suspected PE.

RESEARCH QUESTIONS

The proposed HTA will address the following research questions. Details on the specific interventions and outcomes are included in Table 1.

Clinical

To acknowledge the order of assessment in the diagnostic pathway (note: a diagnostic pathway is defined for this report as a specific and deliberate sequence of assessments comprising strategies for initial risk stratification and ultimate determination of disease positivity. This is distinct from the use of the term “diagnostic imaging studies,” which applies only to CT, magnetic resonance imaging [MRI], V/Q, PET-CT, and thoracic ultrasound-based studies used to diagnose PE) for PE, the clinical research questions are ordered by intervention, starting with risk stratification strategies, and followed by complete diagnostic pathways and diagnostic imaging studies. This does not reflect the priority of the research questions.

Risk Stratification Strategies

1. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of Wells or Geneva clinical prediction rules for the risk stratification of adult patients presenting with PE symptoms in urban, rural, and remote settings:
    a. with or without the use of PERC
    b. with or without the use of D-dimer testing
    c. with or without the use of other biochemical or imaging risk stratification strategies?

Diagnostic Pathways and Diagnostic Imaging Studies

2. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of diagnostic pathways including imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?
3. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?

Cost-Effectiveness

4. What is the cost-effectiveness of diagnostic pathways, including imaging studies, to test adult patients suspected of PE?

Patient Experiences and Perspectives

5. What are the experiences with the diagnostic process from the perspective of those who have undergone testing for acute PE, as well as their family members and non-clinical caregivers?
6. What are the experiences with diagnostic imaging technologies for hematological, pulmonary, or cardiac conditions from the perspective of patients and their family members and non-clinical caregivers?

Implementation Issues

7. What are the issues associated with implementing the optimal use of diagnostic strategies, including imaging, for acute PE in adults in urban, rural, and remote settings?

Environmental Impacts

8. What are the environmental impacts associated with the use of diagnostic pathways, including imaging studies, for the diagnosis of PE in adults in urban, rural, and remote settings?

Questions 1 through 3 will be addressed through a SR of available clinical evidence, and question 4 will be addressed through a primary economic evaluation. The questions related to patient experiences and perspectives (5 to 6) will be addressed through a rapid review of the relevant qualitative literature. Implementation issues (question 7), and environmental factors (question 8) associated with imaging for PE diagnosis will be addressed through informal literature searches and narrative summaries.

METHODS

SEARCH STRATEGY

The literature search will be performed by an information specialist, using a peer-reviewed search strategy. The complete search strategy is presented in Appendix 1.

For the clinical search for risk stratification studies, published literature will be identified by searching the following databases: MEDLINE (1946–) with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE); Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be PE/VTE and Wells or Geneva clinical prediction rules, PERC, and D-dimer testing.

Methodological filters will be applied to limit retrieval to HTAs, SRs, meta-analyses (MAs), network meta-analyses, and overviews of reviews. Retrieval will be limited to documents published since Jan 1, 2011. The search will also be limited to English- or French-language publications. Conference abstracts will be excluded from the search results.

For the clinical search for diagnostic imaging studies, published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Central Register of Controlled Trials via Ovid; CINAHL via EBSCO; and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be PE/VTE and CT technologies, MRI technologies, V/Q-based technologies, PET-CT and thoracic ultrasound (plus echocardiography).

Methodological filters will be applied to limit retrieval to randomized controlled trials (RCTs) and non-randomized studies. Retrieval will be limited to documents published since Jan 1, 2006. The search will also be limited to English- or French-language publications. Conference abstracts will be excluded from the search results.

Three additional searches will also be performed. Economic studies will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, Embase (1974–) and the NHS Economic Evaluation Database (NHS EED) via Ovid; and PubMed. Methodological filters will be applied to limit retrieval to economic studies. No date limit will be applied. Information related to patient experiences will be identified by searching the following databases: MEDLINE (1946–), Embase (1974–), and PsycINFO (1967–) via Ovid; CINAHL via EBSCO; PubMed and the Social Sciences and Humanities segment in Scopus. Methodological filters will be applied to limit retrieval to qualitative studies. Retrieval will be limited to documents published since January 1, 2006. Implementation-related information will be identified by searching MEDLINE (1946–) and Embase (1974–) via Ovid; CINAHL via EBSCO; PubMed. Retrieval will be limited to documents published since January 1, 2006. These additional searches will be limited to English- or French- language publications. Conference abstracts will be excluded from all searches.

The initial searches will be completed in September 2016. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, patient-related groups, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

CLINICAL REVIEW

This protocol was written a priori and will be followed throughout the review process. Any deviations from the protocol will be disclosed in the final report and updates will be made to the PROSPERO submission accordingly.

Selection Criteria

The selection criteria for research questions 1 through 3 can be found in Table 1. The clinical care pathway is presented in Appendix 5. For the research question (1) addressed by an overview of SRs, the selection criteria apply to the criteria used by the potentially relevant SRs in identifying primary studies to include. For the research questions (2 and 3) addressed by SRs of primary studies, the selection criteria apply to the population, intervention, comparator, outcomes (PICOs) elements of the individual studies.

Table 1: Selection Criteria for Clinical Research Questions

Population	
Q1 to 3: Adult patients ≥ 18 years undergoing testing for acute PE[a] *Subgroups of interest:* • Pregnant women • Patients presenting for assessment at centres with access to imaging versus without access to imaging • Emergency room patients versus in-patients (secondary or tertiary care) • Patients who present with symptoms in the primary care setting • Geographical subgroups (urban, rural, and remote) • Patients with high versus low pretest probability	
Interventions	**Comparators (or Reference Standards)**
Q1: *Risk Stratification*[b]	
Wells or Geneva clinical decision rules ± PERC criteria ± D-dimer ± additional biochemical or imaging-based risk stratification strategies[c]	Q1A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q1 A, B, and C: • Any alternative clinical decision rule or modified or tailored tool (e.g., Wells, Geneva, or other) ± PERC criteria ± D-dimer ± additional biochemical or imaging-based risk stratification strategies[c] • No clinical rule (Gestalt)
Q2 and 3: *Diagnostic Imaging*	

Q2: Any of the below interventions, including at least 1 of any clinical decision rule, and/or biochemical or imaging-based risk stratification strategy)[c] **Q3:** Any of the following imaging studies • CT technologies[d] • MRI technologies • V/Q-based technologies[e] • PET-CT • Thoracic ultrasound (+ echocardiography)	Q2 and 3A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q2 and 3 A, B, and C: • Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk stratification strategies)
Outcomes[f]	
Q1 to 3: A) Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index B) Primary: • Clinical utility (failure rate [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up])[g] Secondary: • Clinical utility (e.g., efficiency,[h] identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes) C) Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])	
Study design	
Q1: SRs with or without an MA, HTAs **Q2 and 3:** A) Diagnostic test accuracy outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, and cross-sectional studies) B) Clinical utility outcomes: RCTs and non-randomized controlled studies (i.e., controlled clinical trials, cohort studies, controlled before-and-after studies, and case-control studies) C) Safety outcomes: in addition to the above-mentioned study designs, non-randomized studies without a control group (excluding non-sequential case series and case reports) will also be included	
Timeframe	
Q1: Publications within the last 5 years (i.e., between January 2011 and September 2016) **Q2 and 3:** Publications within the last 10 years (i.e., between January 2006 and September 2016)	

± = with or without; AUROC = area under the receiver operating curve; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CTA/CTV = computed tomographic angiography in combination with venous-phase imaging; DOR = diagnostic odds ratio; DVT = deep vein thrombosis; HTA = health technology assessment; ICU = intensive care unit; MA = meta-analysis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary embolism; PET-CT = positron emission tomography – computed tomography; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; SR = systematic review; V/Q = ventilation-perfusion.

[a] *Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.*

[b] *For the purposes of this HTA, the term "risk stratification" refers to the determination of the likelihood of PE, rather than the likelihood of adverse events or mortality resulting from PE.*

[c] *Leg compression ultrasound, capnography, electrocardiography, echocardiography, chest radiograph.*

[d] *Excluding single-detector, including CTA/CTV and triple-rule-out CT.*

[e] *Including planar V/Q scan, V/Q SPECT, V/Q SPECT-CT.*

[f] *No restriction on length of follow-up.*

[g] *Morbidity and mortality due to misdiagnosis such as A) morbidity and mortality in false-negative patients (the proportion of*

patients classified as having low risk of PE who receive an ultimate diagnosis of PE based on the reference standard [false-negatives/true-negatives + false-negatives], and B) risk of bleeding in false-positive patients who receive anticoagulation treatment.

[h] *The proportion of patients in the study cohort stratified to the group with low predicted probability of PEs (sum of true- and false-negatives/total cohort).*

Study Design

An informal scoping review of existing HTAs and SRs identified through a MEDLINE and grey literature search was conducted to inform the preparation of this protocol. Due to the breadth of evidence available regarding risk stratification strategies, it was decided that a systematic overview of existing HTAs and SRs would be appropriate to address research question 1. Based on observed heterogeneity in the scope of existing SRs on diagnostic imaging studies and diagnostic algorithms including imaging studies, it was decided that a systematic review of primary studies would be most appropriate to address research questions 2 and 3. To reflect the differences in the chosen methodological approaches, sections of this protocol will be organized by A) risk stratification (research question 1) and B) diagnostic pathways and imaging studies (research questions 2 and 3).

Risk Stratification

For interventions used for risk stratification of patients with suspected PE (research question 1), a systematic overview of SRs available in the literature on the diagnostic test accuracy, comparative clinical utility, and safety of the interventions of interest will be conducted. All SRs identified that meet selection criteria will be included, including SRs with or without a meta-analysis (MA), as well as HTAs that include an SR with or without an MA.

If SRs are available, no primary studies, including those published after the latest search date of the included SRs, will be included. If no published SRs on any given intervention, comparator, or outcome of interest are identified, a SR of primary studies may be conducted. At that time, a primary review protocol will be developed accordingly and become an addendum to this protocol.

Diagnostic Pathways and Diagnostic Imaging Studies

An SR of primary studies on the diagnostic test accuracy, comparative clinical utility, and safety of diagnostic pathways and imaging studies used for PE diagnosis in adult patients being tested for PE will be conducted to address research questions 2 and 3. Randomized controlled and controlled non-randomized clinical studies will be included. Uncontrolled studies will be included only for studies investigating patient harms. A high-level narrative overview of the results of the aforementioned scoping review of SRs will be presented to provide context for the discussion.

Exclusion Criteria

Risk Stratification

To be included for research question 1, SRs must have the term “systematic review” or “meta-analysis” in the title or elsewhere in the text; include a detailed description of comprehensive selection criteria and search methods (i.e., as described in Assessment of Multiple Systematic Reviews [AMSTAR] checklist item 3, search at least two electronic sources, adequately report years searched and databases used, key words and/or MeSH terms, and where feasible, the search strategy provided); assess the quality (or risk of bias) of included studies; and synthesize the findings quantitatively and/or qualitatively. For studies that meet the other criteria but do not perform a quality assessment of the primary included studies, the studies will be included as SRs if they have relevant outcomes or subgroups that are not present in any of the other included SRs, or if they include unique primary studies not reviewed by another SR. In this case, quality assessment of the primary studies will be conducted *de novo* in duplicate. SRs will be excluded if they do not meet the selection criteria outlined in Table 1, if they are duplicate publications, or if they were published prior to 2006. Multiple publications of the same SR will be excluded unless they provide additional outcomes of interest. Older SRs (based on publication year) identified in the literature search results will be excluded if they are superseded by an updated SR, or if all the included studies in the older SRs are included in newer SRs. However, two SRs that include identical primary studies will be included if they report different outcomes or identical outcomes but present different subgroup analyses. The degree of overlap between SRs with overlapping primary studies will be judged by building a matrix of included studies in the SRs, which will be reported within the results section of a final report. If an SR has unique primary studies, but they are limited to case reports, they will be excluded in the interest of appraising higher-quality evidence and in acknowledgement of design limitations resulting in high risk of bias. Similarly, SRs with unique primary studies that do not meet the inclusion criteria will be excluded if all other studies are included within another SR. A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Diagnostic Pathways and Diagnostic Imaging Studies

For questions being addressed by a review of primary studies (research questions 2 and 3), studies will be excluded if they do not meet the selection criteria outlined in Table 1, if they are case reports, or if they are duplicate publications. If there are multiple publications of the same study, the less recent will be excluded unless it provides additional information on the outcomes of interest. There is no restriction regarding the duration of time between symptom presentation and assessment, or length of follow-up. Studies will be excluded if they are not published in English or French. Further, conference abstracts, published thesis documents, and evidence that have not been peer-reviewed will not be included.

Screening and Selecting Studies for Inclusion

Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search, reference lists of identified eligible studies, and any articles identified by content experts. This will be followed by an independent review of the full-text articles selected by the two reviewers, based on the pre-determined selection criteria outlined in Table 1. The two reviewers will compare their selections from the full-text review and resolve disagreements through discussion until consensus is reached, consulting a third reviewer if necessary. A final draft list of included studies will be posted for stakeholder review for 15 business days, and feedback and any additional studies identified for potential inclusion will be reviewed following the above process.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[48] will be used to report the study selection process. A full-text screening checklist is reported in Appendix 2.

Data Extraction

Standardized data extraction forms (Appendix 3; Appendix 4) have been designed a priori to document and tabulate all relevant information from included studies. Relevant information includes both descriptive data and results reported in all included studies. Two reviewers will pilot the extraction forms in duplicate among pairs of randomly selected included studies until consistency between reviewers is reached.

Once consistency is reached, data from each included study will be extracted by one reviewer and checked for accuracy by a second reviewer (i.e., the studies will be randomly divided into two independent groups of equal size, one of which will be extracted by one reviewer and the other by another reviewer. Each reviewer will then verify the data extracted from the group of studies they did not extract). Disagreements will be resolved through discussion, involving a third reviewer, if necessary. Data will not be extracted from figures if they do not explicitly provide numerical data. For SRs, primary studies will be consulted for any missing information, to clarify any issues, or to verify extracted data, if necessary. Authors of the studies included in this review will be contacted to provide any missing information or clarify any issues.

Methodological Assessments

Risk Stratification

For question 1, which is being addressed by an overview of SRs, the Risk of Bias in Systematic Reviews (ROBIS) tool,[49] designed to assess the risk of bias in SRs of RCTs and non-randomized studies will be used. Although the results of the methodological assessments will not be used to exclude the included SRs, the conclusions and discussion of the final report will focus on the findings of the SRs of higher quality.

Two reviewers will pilot the quality assessment tools on pairs of two randomly chosen studies and, once consistency in assessments is reached, then independently assess the methodological quality of the remaining included studies. Disagreements will be resolved through discussion, involving a third reviewer, if necessary.

Diagnostic Pathways and Diagnostic Imaging Studies

For the questions (research questions 2 and 3) being addressed by an SR of primary studies, clinical RCTs will be assessed using the Cochrane Risk of Bias Tool.[50] Clinical non-randomized studies will be assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies (ROBINS-I).[51] Studies assessing diagnostic test accuracy will be evaluated used the QUADAS-II instrument.[52] The results of the methodological assessments will not be used to exclude primary studies, but the conclusions and discussion of the final report will focus on the findings of the studies of higher quality.

Summary of Evidence

Description of Study Characteristics and Findings

Risk Stratification

A summary of SR characteristics — including the total number of SRs by population, intervention, comparator, outcomes, and study design (PICOS) elements, countries and years of publication, and findings — will be provided. Additionally, information from SRs — including characteristics, numbers, types, and years of publication of primary studies included in the SRs — will be summarized. In the case that more than one SR is included for a given intervention, the comparator(s), and outcome(s) of interest, and any overlap of included studies among SRs will be described and presented (e.g., by preparing a matrix of included studies in the SRs).

Diagnostic Pathways and Diagnostic Imaging Studies

A summary of primary study characteristics — including the total number of studies by PICOS elements, and countries and years of publication — will be provided in the form of tables and a narrative summary.

Description of Methodological Assessments

A narrative summary of the results of methodological assessment for each included study will be provided. Specifically, tables will be developed to present the answers to the questions within the respective assessment tools, with symbol codes to distinguish between classifications. A narrative description of the strengths and limitations of the included studies will be presented within the main text of the report to provide the reader with an overview of the quality of the literature and to highlight any nuances not addressed in the methodological assessment tables.

Narrative Synthesis

Risk Stratification

A narrative synthesis of the results of included SRs will be conducted for research question 1. The findings will be grouped by outcome, with diagnostic test accuracy, clinical utility, and safety outcomes grouped separately. No re-synthesis of the findings from primary studies will be conducted. Results will be represented as reported in SR study reports, including a summary estimate and confidence interval (CI), measure of heterogeneity, and number of studies and participants contributing to each estimate, as available. Tables will be developed to present results by outcome. This is intended to accompany the narrative summary, to ensure consistency of presented information across all included SRs and to facilitate comparisons by the reader. Results will be synthesized by outcome for the overall study population, and also for each subgroup listed in Table 1.

Diagnostic Imaging Studies

In addition to the SR of primary studies described above, a narrative synthesis of the results of the scoping review of SRs on diagnostic imaging studies will be presented to contextualize the findings of the primary study review conducted for questions 2 and 3. The findings will be grouped by outcome, with diagnostic test accuracy, clinical utility, and safety outcomes grouped separately. No re-synthesis of the findings from primary studies will be conducted. Results will be represented as reported in SR study reports, including a summary estimate and CI, measure of heterogeneity, and number of studies and participants contributing to each estimate, as available. Tables will be developed to present results by outcome. This is intended to accompany the narrative summary, to ensure consistency of presented information across all included SRs and to facilitate comparisons by the reader. Results will be narratively synthesized by outcome for the overall study population, and also for each subgroup listed in Table 1.

Statistical Analysis

Data Synthesis Methods

The results of studies included for questions addressed by a SR of primary studies (questions 2 and 3) will be pooled using MA, if appropriate. The decision to pool all studies or subsets of studies will be made after review and exploration of heterogeneity. Clinical and methodological heterogeneity will be assessed in consultation with the clinical experts. This assessment will consider patient and study design factors that might be expected to affect test performance. This will include assessment of heterogeneity of composite reference standards used in the primary studies. If pooling is not appropriate, due to significant clinical heterogeneity, or methodological or statistical heterogeneity that cannot be addressed analytically, the findings will be synthesized narratively.

For each outcome of interest, analysis will be conducted for the overall study population and also for each subgroup listed in Table 1, as the data permit.

Meta-Analysis of Diagnostic Test Accuracy Studies

Based on the scoping review, studies that assessed diagnostic accuracy varied in terms of their applied reference standards, diagnostic pathways, settings, and patient populations. Thus, it is unclear whether pooling will be appropriate. If MA is deemed inappropriate, studies that report on diagnostic accuracy will be reviewed and results will be reported narratively.

Between-study heterogeneity within groups of studies being considered for pooling will be assessed, using graphical presentations including forest plots and plots of sensitivity and specificity in ROC-space, and calculation of between-study variance t^2, summary and predictive CIs.[53]

Reasons for observed heterogeneity will be explored by subgroup or multivariate regression analyses, given the availability of covariate data. Individual comparisons will be summarized separately, and the consistency assessed. Additional sensitivity analyses dealing with study outliers, study size, study quality, study design, and other study- or design-related factors will also be considered to establish the robustness of findings. As some variation in patient population and associated prevalence of PE is anticipated, risk of verification bias as determined during critical appraisal will be assessed in sensitivity analysis. If substantial verification bias is detected, models will be adjusted using the method of de Groot et al.[54]

There are no established thresholds to determine the appropriateness of pooling of diagnostic testing studies,[53] so the findings of the above will be appraised in terms of usefulness in answering our clinical and policy questions. Should we decide that MA is appropriate, we will use the model developed by Rutter and Gatsonis to generate hierarchical summary receiver operating characteristic (HSROC) curves,[55] as well as pooled sensitivity, specificity, diagnostic odds ratio (DOR) values, and their 95% CIs. The area under the curve (AUC) will be used as a quantitative measure of the diagnostic accuracy of imaging studies for PE diagnosis, with values closer to 1 indicating better diagnostic performance, and a value closer to 0.5 indicating poor performance.[56] Positive and negative likelihood ratios above 10 and below 0.1, respectively, will indicate low misdiagnosis rates.

In the event that we observe substantial variation in reference standards between studies put forth for pooling, particularly involving composites of multiple tests, we will use an extension of the Rutter and Gatsonis model that allows imperfect and composite reference standards.[57,58] Unknown parameters will be estimated using a Bayesian approach with non-informative prior distributions, which allow the observed data to dominate the final estimates of sensitivity and specificity. Our models will assume independence of the combined tests acknowledging evidence that suggests the results may be affected if tests show dependency.[59,60]

Exploration of heterogeneity, plotting, and MA will be conducted using the statistical software R,[61] with packages *mada*[62] and *HSROC*.[63]

If pooling is not appropriate, a narrative synthesis will include the presentation of findings within summary tables, alongside study and clinical characteristics believed to contribute to heterogeneity, as determined during the exploration of the data. A narrative description will aim to synthesize observed test performance in the absence of an MA.

Meta-Analysis of Primary Clinical Utility and Safety Studies

The clinical utility of risk stratification strategies and imaging studies for PE diagnosis will be based on findings about the benefits (e.g., diagnostic efficiency, influence on choice of treatment and subsequent reduced exposure to imaging harms or harms of unnecessary intervention, and the indirect effect on clinical outcomes), and harms (e.g., failure rate).

Dichotomous outcomes (e.g., mortality) will be summarized, using relative risks and 95% CIs (or odds ratios and 95% CIs, if case-control studies are included). Continuous outcomes will be summarized, using differences in means and 95% CIs, if appropriate. If indicated (e.g., for quality-of-life scales), standard methods for converting between units of measurement will be used, and we will calculate standardized mean differences if possible. For outcomes reported as time-to-event and given available individual patient data in the form of a survival curve or table of events per patients at risk, analyses will be performed, using Kaplan–Meier curves and Cox regression. If studies report adjusted effects measures, the adjusted results in the primary analysis will be used, with the unadjusted result in exploratory analyses presented and comments on any differences between the two. If required measures of variance are not available, variances will be imputed if possible.[64] Forest plots will be shown for all individual summary estimates. Findings will be reported as “not statistically significant” if the 95% CI of the overall estimate includes unity for dichotomous data or includes 0 for continuous data.

Between-study heterogeneity within groups of studies being considered for pooling will be assessed, using graphical presentations (including forest plots and plots of outcomes against covariates), and calculations of the I^2 and Cochran’s Q test statistic. An $I^2 \geq 75\%$ will be interpreted to indicate considerable heterogeneity across studies, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*. Cochran’s Q test statistic — based on chi-squared, where I^2 = (Q-degrees of freedom)/Q — will be based on a level of significance of 10%. Clinical and methodological heterogeneity will be assessed in

consultation with the clinical experts.

Reasons for observed heterogeneity will be explored by subgroup or multivariate regression analyses, given the availability of the data. Individual contrasts will be summarized separately, and the consistency assessed. Additional sensitivity analyses dealing with study outliers, study size, study quality, study design, and other study- or design-related factors will also be considered to establish the robustness of findings.

If pooling of outcome data is appropriate, summary measures and CIs for the reported outcomes will be reported. Random-effects models will be used. In the event that both randomized and non-randomized studies report on the same outcome, RCTs will be considered separately from non-randomized studies. The influence of study design will be explored in sensitivity analyses. MAs would be carried out using the Cochrane Review Manager software, version 5.3, or using R with package *metafor*.[65]

If pooling is not appropriate, a narrative synthesis will include the presentation of findings within summary tables, alongside study and clinical characteristics believed to contribute to heterogeneity, as determined during the exploration of the data. A narrative description will aim to synthesize the direction and size of any observed effects across studies in the absence of a MA and will include an assessment of the likelihood of clinical benefit or harm.

Publication bias will be assessed using visual funnel plots, and tested using Egger's regression test and Begg's rank correlation test.[66]

Network Meta-Analysis

The results of studies assessing the diagnostic accuracy of diagnostic imaging studies for PE diagnosis (questions 2 and 3) will be pooled, using network meta-analysis (NMA), if appropriate. Methods will be further developed in consultation with an expert if it is deemed possible to conduct the NMA. The scope of this analysis is presented in Appendix 6. All possible comparisons between diagnostic imaging studies (interventions) of interest will be evaluated.

ECONOMIC REVIEW

A primary economic analysis on the cost-effectiveness of different diagnostic strategies in adults suspected of acute PE will be conducted to address research question 4.

Primary Economic Analysis

A decision-analytic model will be developed to assess the costs and health outcomes associated with diagnostic strategies in patients suspected of acute PE.

In particular, the risk stratification and diagnostic imaging strategies of interest may include the following:

Risk stratification: (i.e., series of clinical decision rules with or without biochemical and/or imaging-based strategies to assign risk of PE)

i. Clinical decision rule:
    a. Wells score
    b. Geneva rule
ii. If patients are deemed low risk of PE from the clinical decision rules, the following tests may be further conducted:
    a. D-dimer testing
    b. PERC

Diagnostic imaging technologies:

i. CT technologies
ii. MRI technologies
iii. V/Q-based technologies
iv. PET-CT
v. Thoracic ultrasound (plus echocardiography)
vi. Combinations of the above diagnostic imaging tests

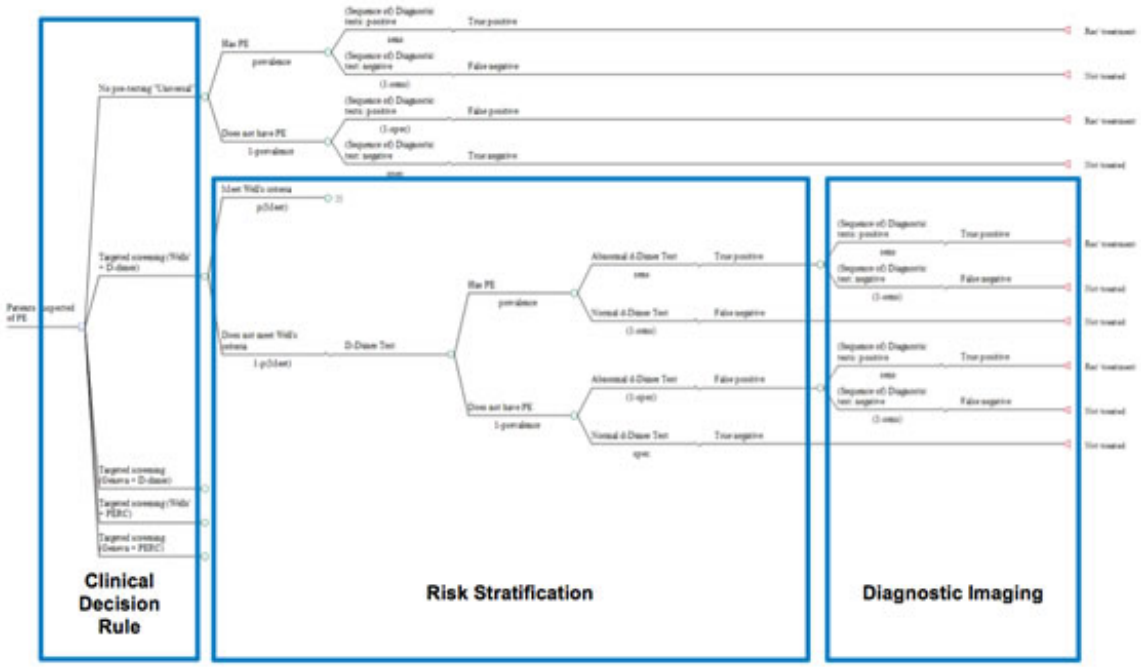
The list above represents the potential diagnostic algorithms that may be compared in the economic analysis. The final diagnostic strategies to be evaluated in the economic analysis will be determined according to the findings of the clinical review.

Model Design

A hybrid model structure will be developed, entailing a decision tree (to capture the implications of the diagnostic strategy) and a subsequent Markov cohort model (to capture the long-term implications of the diagnosis results in terms of initiating and continuing medical treatment).

The patient cohort, suspected of PE, will enter the model. The proportion of patients that will subsequently undergo diagnostic imaging will be based on the properties of the risk stratification assessment and the underlying prevalence of PE within the population. Patients who meet the screening criteria will proceed with diagnostic imaging, while patients with a low post-test probability following the risk stratification assessment will not undergo additional imaging. The sensitivity and specificity of each test, or sequence of tests, will affect the diagnosis of PE. Together, the diagnostic accuracy of the risk stratification assessment and diagnostic imaging tests will affect the true- and false-positive and -negative results (Figure 1).

Figure 1: Sample of Proposed Model Structure on Diagnostic Strategies, Combining Upfront Risk Stratification Strategies and Diagnostic Imaging Test in Adult Patients Suspected of Pulmonary Embolism

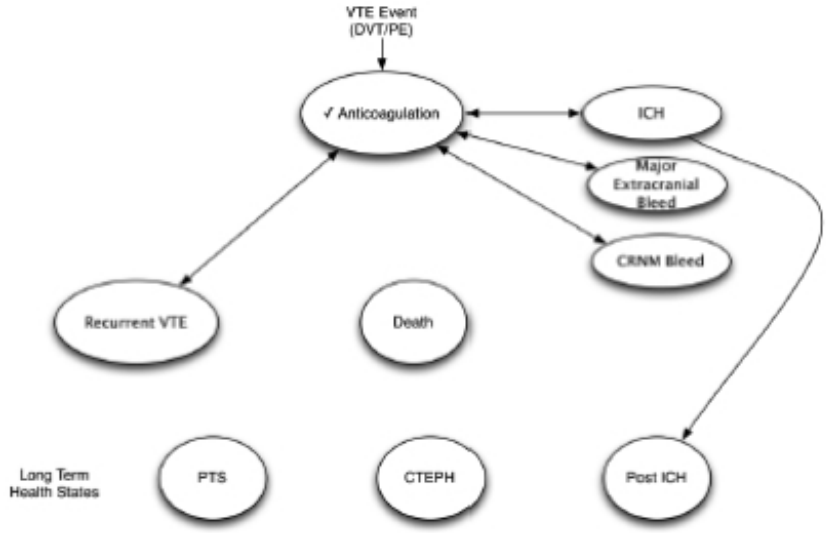


PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria.
Note: Although not explicitly shown, the sequence for the other targeted screening strategies resembles the targeted screening strategy shown for Wells.

Depending on the outcomes of the diagnostic strategies, patients will enter into a Markov model.[67] An existing model that was originally developed to model anticoagulant therapy in patients with VTE will be adapted to reflect PE only. Patients diagnosed with PE will receive treatment, whereas those not diagnosed with PE will receive no treatment.

Figure 2 outlines the structure of the Markov state transition model. Health states in the model included intracranial hemorrhage, severe extracranial or clinically relevant non-major bleeding, recurrent PE, and death.

Figure 2: Conceptual Design of the Markov Component of the Economic Model



CRNM = clinically relevant non-major; CTEPH = chronic thromboembolic pulmonary hypertension; ICH = intracranial hemorrhage, PTS = post-thrombotic syndrome; VTE = venous thromboembolism.
Note: Patients diagnosed with PE enter "anticoagulation" state. After each cycle, patients may move from one health state to the next as indicated by the arrows.
Source: CADTH, 2016.[67]

Based on feedback from the CADTH clinical team and the clinical co-authors, the upfront decision tree for screening will be developed while the downstream pre-existing Markov model for treatment may be further adapted. In addition, clinical experts and members of the Health Technology Expert Review Panel (HTERP) will be consulted as a means of ensuring that the model structure reflects existing clinical literature and Canadian clinical practice. Checks on the internal and external validity of the model will be performed to assess for any logical discrepancies. The decision-analytic model will be constructed in Microsoft Excel 2010.

Perspective

The primary perspective in the model will be that of a publicly funded health care system (i.e., provincial Ministry of Health).

Resource Use and Cost Data

The costs captured will reflect the perspective of the analysis. These costs include those of the diagnostic tests, treatments arising from true or missed diagnosis, and any medical costs related to the treatment of adverse events. Treatment for PE will be based on the patient's PE diagnosis.

Canadian-specific costs will be used, when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2016 Canadian dollars, using the health care component of the consumer price index.

Utilities

Utilities associated with each health state will be obtained from the literature and from Canadian sources when possible.

Clinical Parameters

Diagnostic accuracy: The diagnostic accuracy of each strategy (e.g., sensitivity and specificity) will be obtained from the clinical review. Estimates of the rates of adverse events associated with each strategy will similarly be informed from the clinical review.

Natural history: The underlying prevalence of PE will be varied in the analysis. The natural history of patients with PE will be based on an existing economic evaluation.[67] The parameters values may be further modified to reflect the findings from the clinical review if they are determined to be more relevant.

Outcomes

The model will estimate the expected costs, quality-adjusted life years (QALYs), correct and missed diagnoses, and the mortality incidences for different combinations of screening and diagnostic strategies for PE over the model time horizon. QALY will be the primary clinical outcome measurement, as this single measure captures the impacts of both morbidity and mortality. The primary results of this model will be the incremental cost-effectiveness ratios (ICERs), measured in terms of the incremental costs per QALY gained, of the diagnostic strategies on the efficiency frontier. A secondary calculation for the ICER, based on the incremental cost per life saved, will also be determined.

Time Horizon and Discounting

As the impact of screening for PE may have long-term treatment consequences depending on a patient's risk for recurrent events, a lifetime time horizon will be considered. Alternative time horizons will be assessed in sensitivity analyses (e.g., six months).

As per existing guidelines, discounting will be set at 5% per year for both costs and QALYs with sensitivity analysis conducted on this value.[68]

Sensitivity Analysis

The base-case analysis will represent the probabilistic findings, capturing the impact of parameter uncertainty, with results presented on the cost-effectiveness acceptability curve (CEAC). The CEAC will highlight interventions on the efficiency frontier across different willingness-to-pay thresholds. Uncertainty in the model will be further evaluated in a number of ways. Scenario and subgroup analysis will be performed to evaluate key model assumptions, while retaining the probabilistic element of the model. Potential scenarios and subgroups of interest may include:

- Setting: urban, rural or remote communities
- Hospital setting: in-patient versus outpatient
- Pregnant females
- Pretest probability level for PE.

Other analyses to address parameter uncertainty may include varying sets of related inputs (e.g., sensitivity and specificity of diagnostic strategies) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

Assumptions

During the course of the development of the model, assumptions and limitations will be identified and acknowledged in the report. Where possible, assumptions will be tested through the conduct of appropriate sensitivity analyses.

PATIENT PERSPECTIVES AND EXPERIENCES

Study Design

A Rapid Response Summary with Critical Appraisal of the qualitative literature will be conducted describing the perspectives of people who have undergone testing for acute PE, or testing with the diagnostic imaging technologies included in this review for other pulmonary, hematological, or cardiac conditions. The perspectives of family members, and other non-clinical caregivers, will be considered.

The final report will include a summary of the evidence, study characteristics, and findings, as well as a brief statement on implications for decision-making or policy-making.

Selection Criteria and Methods

One reviewer will screen citations identified through the literature search. In the first level of screening, titles and abstracts will be reviewed and the full text of potentially relevant articles will be retrieved and assessed for inclusion by the same reviewer. The final selection of full-text articles will be based on the inclusion criteria in Table 2. The study selection process will be presented in a PRISMA flow chart.[48]

Table 2: Selection Criteria for Patient Preference and Experience Questions

Population	Q5: Adults (≥ 18 years), and their non-clinical caregivers (e.g., partners and family members), who have undergone testing for suspected acute PE using any strategy. Q6: Adults (≥ 18 years), and their non-clinical caregivers (e.g., partners and family members), who have experience with eligible diagnostic imaging technologies for hematological, pulmonary, or cardiac conditions
Intervention	Q5: Any pathway used for diagnosing acute PE (e.g., Wells, D-dimer, imaging) Q6: CT technologies, MRI technologies, V/Q-based technologies, PET/CT, thoracic ultrasound
Comparator	Q5 to 6: No comparator necessary
Outcomes	Q5 and Q6: Experiences of benefits and harms; expectations versus actual experiences; outcomes of importance to patients and caregivers; value of outcomes from the perspective of patients and caregivers; any other outcome of importance to patients and caregivers that might emerge from the literature
Study Designs	SRs of qualitative studies, qualitative studies of any design, and mixed methods studies

CT = computed tomography; MRI = magnetic resonance imaging; PE = pulmonary embolism; PET = positron emission tomography; Q = research question; SR = systematic review; V/Q = ventilation-perfusion.

Exclusion Criteria

To be eligible, studies must explore or assess the perspectives of patients and caregivers directly and not indirectly; for example, through another person. Studies that assess only clinician perspectives will be excluded. The following types of publications will also be excluded: theses and dissertations, data presented in abstract form only, book chapters, editorials, and letters to the editor. Studies will be excluded if they are not published in English.

Data Extraction

Data collection will involve extracting data regarding study characteristics and study results from primary reports, as relevant to the research question. From each eligible article, descriptive data will be extracted by one reviewer into a standardized electronic form. Descriptive data will include such items as first author, article title, study objectives, participant characteristics, and study design. Result statements from the eligible articles relevant to the research question will be captured for analysis using NVivo qualitative data analysis software (QSR International Pty Ltd. version 11, 2015). Result statements are typically presented within the “results” section of a report and are characterized as data-driven and integrated findings based on participant experiences. Before being coded, each result statement will be assessed to ensure it is differentiated from raw data, methods, external data, and researchers’ conclusions and implications. The latter will not be coded. Only results presented within the main report will be coded. Data from figures will not be used unless data points are explicitly labelled.

Quality Assessment

The included qualitative studies will be critically appraised by one reviewer using the Critical Appraisal Skills Programme (CASP) Qualitative Checklist[69] and the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses as a guide.[70] A summary of the strengths and limitations of each included study will be reported.

Summary of Evidence and Data Synthesis

Description of Study Characteristics

A narrative summary of study characteristics, including the total number of studies by PICOS elements, will be provided, alongside descriptive information including countries and years of publication and sample size. A table will be developed to accompany the narrative summary and to ensure consistency of presented information across all studies and facilitate study comparisons by the reader.

Summary of Critical Appraisal

A narrative summary of the results of the critical appraisal will be presented, including an overall impression of the quality of included studies. Tables will accompany the narrative summary to ensure consistency of presented information across all studies and to facilitate study comparisons by the reader. Tables will present the strengths and limitations of each study, following the criteria used to conduct the critical appraisal.

Content Analysis

A content analysis will be conducted by coding relevant result statements within the included articles line by line, and subsequently organizing the data into common categories.[71] The analysis will be conducted using NVivo qualitative data analysis software; QSR International Pty Ltd. Version 11, 2015.[72] The content analysis will be conducted by a single reviewer, who will maintain extensive field notes and a study journal to memo emerging insights, and how the analysis evolves. Regular meetings with the study team will serve a peer-debriefing and peer-review function, to challenge emerging ideas and help ensure the analysis stays close to the data.

Coding will begin with an a priori "start list" of codes developed based on the research questions; for example, perceived benefits and harms, challenges, and psychological and physical distress. As coding progresses, other codes not on the start list will emerge inductively to capture unexpected meaning and content grounded in the results themselves. When new codes emerge, all data will be recoded to search for further instances of the meaning captured by that code.

Once all data have been coded, the codes will be organized into related areas to construct descriptive categories that represent and encompass codes with similar meanings. In this process, the reviewer will look for similarities and differences between codes and group together similar codes. Once categories have been identified, a draft definition of each code and category will be written by the reviewer. Descriptions of the data within each code and category will also be prepared, and these will remain close to the data with minimal interpretation. Where apparent, differences between various populations — for example, men and women or older and younger people — will be noted in these descriptions. Exemplar quotations will also be included, if appropriate.

IMPLEMENTATION ISSUES

There are many challenges in the diagnosis of PE. These challenges can lead to the less-than-optimal use of medical imaging or other diagnostic strategies for suspected PE and, in turn, to the missed diagnosis, misdiagnosis, or over-diagnosis of the condition. Implementing the optimal use of diagnostic strategies for acute PE faces its own challenges, which will be assessed and discussed in this report.

Study Design

An information specialist will develop a peer-reviewed search strategy for a targeted literature search to identify information on the factors that influence the use of optimal strategies for the diagnosis of PE (as identified by the clinical research questions). These factors may include enablers or facilitators — things that support or promote the optimal use of strategies for the diagnosis of PE — as well as barriers: those factors that impede the optimal use of strategies for the diagnosis of PE. Special attention will be paid to the differing issues between academic tertiary care centres, urban hospitals, rural hospitals, and remote settings. For example, the issues may include:

- Technical requirements, resource needs and availability, logistical considerations, and operational constraints
- Staffing, training, and accreditation issues (e.g., clinical specialties)
- Referral pathways.

Based on our initial findings and review of the literature, further targeted searches to identify additional information influencing the implementation of optimal strategies for the diagnosis of PE may be carried out. If gaps are identified where no information is available in the literature, alternative means for gathering information on implementation will be considered and could include surveys, focus groups, an environmental scan, or an analysis of the attitudes, behaviours, and beliefs of clinicians associated with diagnosing PE (i.e., a current practice analysis).

Data Extraction

From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention information, and implementation issues identified will be captured by one reviewer.

Descriptive Analysis

Information from relevant studies will be organized according to the population and imaging modality. This information will be summarized narratively by one reviewer.

ENVIRONMENTAL IMPACTS

Study Design

A narrative literature review on the potential environmental impacts associated with different interventions for the diagnosis of PE in adults will be conducted.

Selection Criteria

Articles that provide insight on potential environmental impacts associated with strategies for the diagnosis of PE, in Canadian contexts, will be included. For example, the impacts may relate to resource use and waste management.

Screening and Selection of Articles for Inclusion

Citations arising from the literature searches conducted to address other research questions that discuss or present environmental issues relevant to diagnosis of PE will be included.

Data Extraction

From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention, and potential environmental impacts identified will be captured by one reviewer in an Excel spreadsheet.

Descriptive Analysis

Information from relevant studies will be organized according to theme. This information will be summarized narratively by one reviewer.

AREAS FOR POTENTIAL AMENDMENTS

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Sept 2016
Alerts:	Monthly search updates until project completion
Study Types:	**Risk Stratification search**: Health technology assessments; systematic reviews; meta-analyses; network meta-analyses. **Diagnostic Imaging search**: randomized controlled trials; non-randomized studies
Limits:	Date limit: **Risk Stratification search:** 2011-present Date limit: **Diagnostic Imaging search:** 2006-present Language limit for both searches: English- and French-language Conference abstracts: excluded from both searches

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading

SYNTAX GUIDE	
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

#	Risk Stratification Search
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	Fibrin Fibrinogen Degradation Products/
8	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kf.
9	Decision Support Techniques/
10	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kf.
11	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
12	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
13	(rule out or decision or prediction).ti.
14	or/7-13
15	6 and 14
16	15 use pmez
17	lung embolism/
18	pulmonary embolism/
19	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kw.
20	Venous Thromboembolism/
21	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
22	VTE.ti,ab,kw.

#	Risk Stratification Search
23	or/17-22
24	fibrin degradation product/ or D dimer/
25	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kw.
26	decision support system/
27	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kw.
28	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
29	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
30	(rule out or decision or prediction).ti.
31	or/24-30
32	23 and 31
33	32 use oemezd
34	33 not conference abstract.pt.
35	16 or 34
36	meta-analysis.pt.
37	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
38	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
39	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
40	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
41	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
42	(handsearch* or hand search*).ti,ab,kf,kw.
43	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
44	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
45	(meta regression* or metaregression*).ti,ab,kf,kw.
46	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
47	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
48	(cochrane or (health adj2 technology assessment) or evidence report).jw.
49	(meta-analysis or systematic review).md.
50	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
51	(outcomes research or relative effectiveness).ti,ab,kf,kw.
52	((indirect or indirect treatment or mixed treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
53	(network* adj3 (meta-analys* or metaanalys*)).ti,ab,kf,kw.
54	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
55	umbrella review*.ti,ab,kf,kw.
56	nma.ti,ab,kf,kw.
57	(Multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
58	(Multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
59	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
60	MPES.ti,ab,kw,kf.

#	Risk Stratification Search
61	or/36-60
62	35 and 61
63	limit 62 to (english or french)
64	limit 63 to yr="2011 -Current"
65	remove duplicates from 64

#	Diagnostic Imaging Search
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
8	((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).ti,ab,kf.
9	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
10	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
11	or/7-10
12	exp Magnetic Resonance Imaging/
13	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
14	12 or 13
15	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
16	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
17	(ventilation-perfusion adj5 (imag* or scan* or SPECT)).ti,ab,kf.
18	("ventilation/perfusion" adj5 (imag* or scan* or SPECT)).ti,ab,kf.
19	((ventilation and perfusion) adj5 (imag* or scan* or SPECT)).ti,ab,kf.
20	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj5 (imag* or scan* or SPECT)).ti,ab,kf.
21	or/15-20
22	Positron-Emission Tomography/
23	(PET adj3 (scan* or imag*)).ti,ab,kf.
24	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
25	or/22-24
26	exp Lung/us
27	exp Ultrasonography/
28	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
29	or/27-28

#	Diagnostic Imaging Search
30	exp lung/
31	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
32	or/30-31
33	29 and 32
34	exp Echocardiography/
35	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scanning or myocardium scanning or ultrasound cardiography).ti,ab,kf.
36	or/26,33-35
37	11 or 14 or 21 or 25 or 36
38	6 and 37
39	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
40	Randomized Controlled Trial/
41	exp Randomized Controlled Trials as Topic/
42	"Randomized Controlled Trial (topic)"/
43	Controlled Clinical Trial/
44	exp Controlled Clinical Trials as Topic/
45	"Controlled Clinical Trial (topic)"/
46	Randomization/
47	Random Allocation/
48	Double-Blind Method/
49	Double Blind Procedure/
50	Double-Blind Studies/
51	Single-Blind Method/
52	Single Blind Procedure/
53	Single-Blind Studies/
54	Placebos/
55	Placebo/
56	Control Groups/
57	Control Group/
58	(random* or sham or placebo*).ti,ab,hw,kf,kw.
59	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
60	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
61	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
62	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
63	allocated.ti,ab,hw.
64	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
65	or/39-64
66	Epidemiologic Methods/
67	exp Epidemiologic Studies/
68	Observational Studies as Topic/

#	Diagnostic Imaging Search
69	Clinical Studies as Topic/
70	(Observational Study or Validation Studies or Clinical Study).pt.
71	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
72	cohort*.ti,ab,kf.
73	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
74	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
75	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
76	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.
77	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
78	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
79	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.
80	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
81	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
82	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
83	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.
84	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.
85	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
86	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
87	case series.ti,ab,kf.
88	or/66-87
89	65 or 88
90	38 and 89
91	90 use pmez
92	lung embolism/
93	pulmonary embolism/
94	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kw.
95	Venous Thromboembolism/
96	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
97	VTE.ti,ab,kw.
98	or/92-97
99	exp computer assisted tomography/
100	((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).ti,ab,kw.
101	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
102	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
103	or/99-102
104	exp nuclear magnetic resonance imaging/

#	Diagnostic Imaging Search
105	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
106	104 or 105
107	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
108	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
109	(ventilation-perfusion adj5 (imag* or scan* or SPECT)).ti,ab,kw.
110	("ventilation/perfusion" adj5 (imag* or scan* or SPECT)).ti,ab,kw.
111	((ventilation and perfusion) adj5 (imag* or scan* or SPECT)).ti,ab,kw.
112	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj5 (imag* or scan* or SPECT)).ti,ab,kw.
113	or/107-112
114	positron emission tomography/
115	(PET adj3 (scan* or imag*)).ti,ab,kw.
116	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
117	or/114-116
118	exp echography/
119	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
120	or/118-119
121	exp lung/
122	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
123	or/121-122
124	120 and 123
125	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scanning or myocardium scanning or ultrasound cardiography).ti,ab,kw.
126	exp echocardiography/
127	or/124-126
128	103 or 106 or 113 or 117 or 127
129	98 and 128
130	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
131	Randomized Controlled Trial/
132	exp Randomized Controlled Trials as Topic/
133	"Randomized Controlled Trial (topic)"/
134	Controlled Clinical Trial/
135	exp Controlled Clinical Trials as Topic/
136	"Controlled Clinical Trial (topic)"/
137	Randomization/
138	Random Allocation/
139	Double-Blind Method/
140	Double Blind Procedure/

#	Diagnostic Imaging Search
141	Double-Blind Studies/
142	Single-Blind Method/
143	Single Blind Procedure/
144	Single-Blind Studies/
145	Placebos/
146	Placebo/
147	Control Groups/
148	Control Group/
149	(random* or sham or placebo*).ti,ab,hw,kf,kw.
150	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
151	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
152	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
153	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
154	allocated.ti,ab,hw.
155	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
156	or/130-155
157	observational study/
158	cohort analysis/
159	longitudinal study/
160	follow up/
161	retrospective study/
162	exp case control study/
163	cross-sectional study/
164	quasi experimental study/
165	prospective study/
166	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
167	cohort*.ti,ab,kw.
168	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kw.
169	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kw.
170	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kw.
171	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kw.
172	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kw.
173	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
174	(population adj3 (study or studies or analysis or analyses)).ti,ab,kw.
175	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
176	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
177	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kw.
178	((natural adj experiment) or (natural adj experiments)).ti,ab,kw.
179	(quasi adj (experiment or experiments or experimental)).ti,ab,kw.

#	Diagnostic Imaging Search
180	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
181	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kw.
182	case series.ti,ab,kw.
183	or/157-182
184	156 or 183
185	129 and 184
186	185 use oemezd
187	186 not conference abstract.pt.
188	91 or 187
189	limit 188 to (english or french)
190	limit 189 to yr="2006 -Current"
191	limit 190 to yr="2006 - 2010"
192	remove duplicates from 191
193	limit 190 to yr="2011 -Current"
194	remove duplicates from 193
195	192 or 194

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Cochrane Central Register of Controlled Trials	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Grey Literature

Dates for Search:	Sept 2016
Keywords:	Pulmonary embolism, venous thromboembolism
Limits:	Publication years 2006 to present

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for searching health-related grey literature” (https://www.cadth.ca/grey-matters), will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)

- Internet Search
- Open Access Journals.

APPENDIX 2: CLINICAL FULL-TEXT SCREENING CHECKLIST

Reviewer: _____
Date: _____

Ref ID: Author: Publication Year:			
Did the study include:	Yes (Include)	Unclear (Include or exclude)[a]	No (Exclude)
1. Adults (i.e., aged ≥ 18 years), being tested for PE (as per Table 1)	☐	☐	☐
2. The interventions of interest: Risk Stratification Strategies • Wells or Geneva rules • PERC • D-Dimer • Biochemical or imaging studies Imaging • CT-based studies • MRI-based studies • V/Q-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
3. The comparators of interest: Risk Stratification Strategies • Composite reference standard • Any alternative clinical decision rule or modified/tailored tool ± PERC ± D-dimer ± biochemical or imaging-based risk stratification • No clinical rule (Gestalt) Imaging • Composite reference standard • CT-based studies • MRI-based studies • V/Q-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
4. The outcomes of interest: • DTA • Clinical utility • Direct patient harms	☐	☐	☐

Ref ID: Author: Publication Year:			
5. The study designs of interest: • SR • MA • HTA • RCT • NRS • CS	☐	☐	☐
Decision to include the study:[b]	Yes ☐		No ☐
Reason(s) for exclusion:	Inappropriate study population No intervention of interest No or inappropriate comparator No relevant outcomes Irrelevant study design Study description only Other:_____		

CS = case series; CT = computed tomography; DTA = diagnostic test accuracy; HTA = health technology assessment; MA = meta-analysis; MRI = magnetic resonance imaging; NRS = non-randomized study; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria; PET = positron emission tomography; RCT = randomized controlled trial; SR = systematic review; V/Q = ventilation-perfusion.

[a] *This will be discussed with a second reviewer.*

[b] *If all items above are answered "yes" or "unclear," then the study will be included.*

Did the study report any data relevant to another research question (RQ)? ☐ Yes: RQ# _____ ☐ No

APPENDIX 3: CLINICAL DATA EXTRACTION FORM FOR PRIMARY STUDIES

Reviewer: _____
Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

METHODOLOGY	
Study design:	☐ RCT ☐ NRS ☐ CS
Details of study design	
Number of included participants:	
Study eligibility criteria:	
Period of conduct:	

METHODOLOGY	
Setting of conduct:	▢ Emergency room ▢ Secondary or tertiary in-patient care ▢ Primary care ▢ Rural ▢ Remote ▢ Urban
Subgroup analyses	
Multivariate analyses	

CS = case series; NRS = non-randomized study; RCT = randomized controlled trial.

POPULATION	
Age	
Clinical condition or subgroup	▢ Trauma or ICU ▢ Pregnancy ▢ Cancer ▢ Hemodynamically unstable ▢ Oral contraceptive or HRT ▢ Obesity ▢ Renal insufficiency ▢ Allergy to contrast dye ▢ Patients with COPD or pneumonia ▢ Elderly patients ▢ Patients with inherited or acquired thrombophilias
Sex	

COPD = chronic obstructive pulmonary disease; HRT = hormone replacement therapy; ICU = intensive care unit.

COMPARISON	
Intervention (specify disease threshold and cut-off values,[a] manufacturer, technological specifications):	
Comparator (specify disease threshold and cut-off values,[a] manufacturer, technological specifications):	
Duration between index and reference test:	
Occupation or expertise of practitioner administering and interpreting test	

[a] *Including any information about age-specific cut-offs (e.g., for D-dimer)*

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Outcome	
Subgroup analysis	
Variable 1	
Variable 2	
(Add variables as needed)	
Multivariate analysis	
Variable1	
Variable 2	
(Add variables as needed)	
Main conclusions:	

Did the study report any data relevant to another research question (RQ)? ▢ Yes: RQ# _____ ▢ No

APPENDIX 4: CLINICAL DATA EXTRACTION FORM FOR SYSTEMATIC REVIEWS

Reviewer: _____
Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

METHODOLOGY	
Study design:	▢ SR ▢ MA ▢ HTA
Number of included studies:	
Total number of participants within studies included in the review:	
Study eligibility criteria:	
Type of included studies:	
Range of publication years of included studies:	
Databases searched:	
Search period:	
Quality assessment tool:	
Subgroup analyses and/or meta-regression:	

HTA = health technology assessment; MA = meta-analysis; SR = systematic review.

COMPARISON	
Intervention (specify disease threshold and cut-off values, manufacturer, technological specifications):	
Comparator (specify disease threshold and cut-off values, manufacturer, technological specifications):	
Duration between index and reference test:	

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

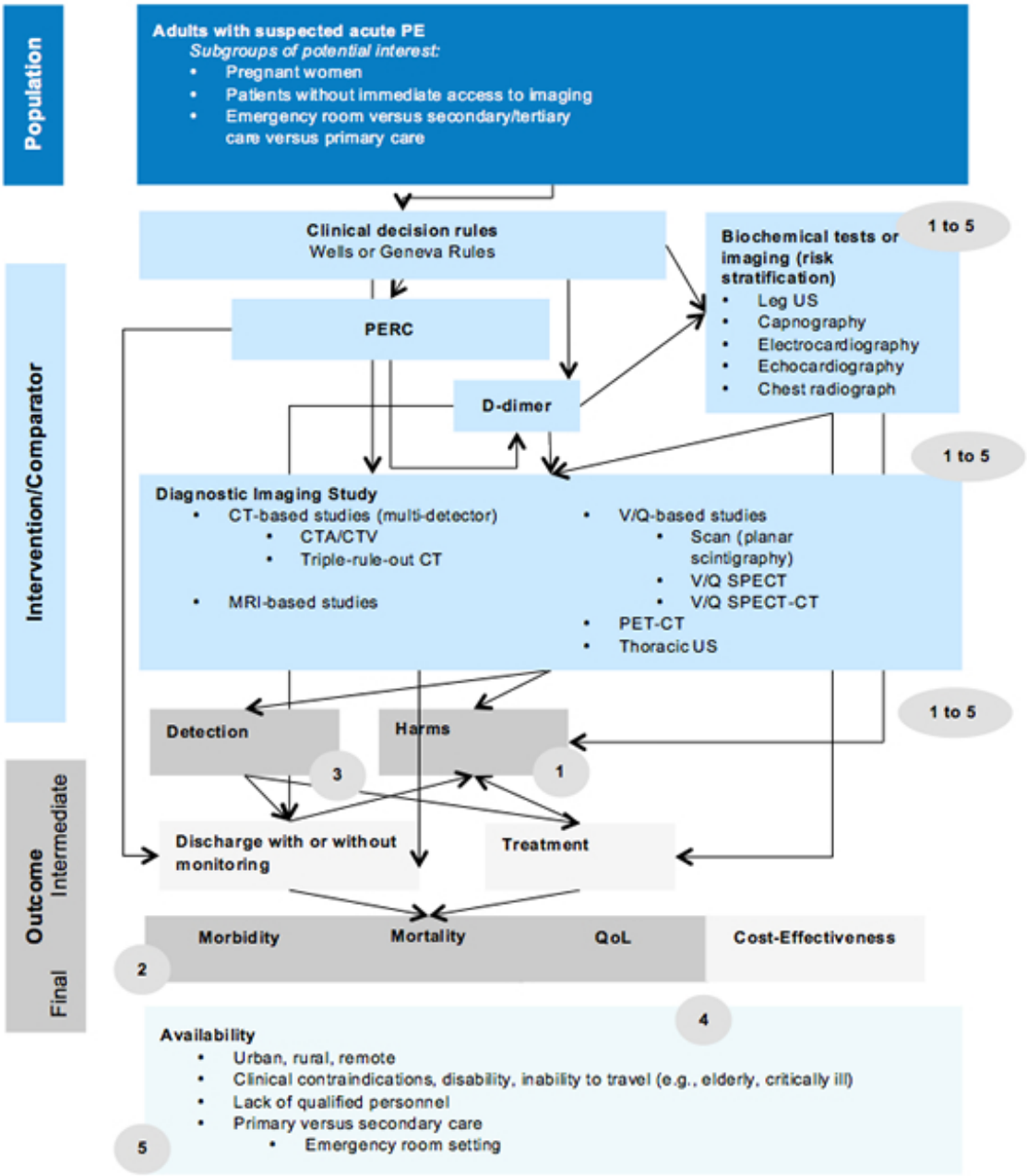
RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	
Outcome	
Study (1st author) [REF ID]	
Number of included studies:	
Range of publication years of included studies:	
Study population (nuances)	
Pairwise MA	
Pooled DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	
NMA	
DTA (95% CI)	
P value for effect	
Subgroups	
Subgroup 1:	
Number of included studies	
DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	
Subgroup 2:	
Number of included studies	
DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
(Add subgroups as needed)	
Meta-regression	
Variables	
Variable 1:	
Variable 2:	
(Add variables as needed)	
Main conclusions:	

CI = confidence interval; DTA = diagnostic test accuracy; MA = meta-analysis; NMA = network meta-analysis.

Did the systematic review report any data relevant to another research question (RQ)? ▢ Yes: RQ# _____ ▢ No

APPENDIX 5: PULMONARY EMBOLISM DIAGNOSIS AND MANAGEMENT STRATEGIES AND SUBSEQUENT OUTCOMES



1	Clinical effectiveness (safety)
2	Clinical utility
3	Diagnostic accuracy
4	Cost-effectiveness
5	Factors influencing modality implementation and use

CT = computed tomography; CTA/CTV = computed tomographic angiography in combination with venous-phase imaging; MRI = magnetic resonance imaging; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria; PET = positron emission tomography; QoL = quality of life; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation-perfusion.

APPENDIX 6: SELECTION CRITERIA FOR NETWORK META-ANALYSIS

Population

Q2 and 3: Adult patients undergoing testing for acute PE[a]

Patient subgroups of interest:

- Pregnant women
- Patients presenting for treatment at centres with access to imaging versus without access to imaging
- Emergency room patients versus in-patients (secondary or tertiary care)

Interventions	Comparators (or Reference Standards)
Any of the following imaging studies (± clinical decision rule ± biochemical or imaging-based risk stratification strategies[b]) • CT technologies[c] • MRI technologies • V/Q-based technologies[d] • PET-CT • Thoracic ultrasound (+ echocardiography)	Q2 and 3A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q2 and 3 A, B, and C: Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk stratification strategies)

Outcomes[e]

Q2 and 3:

A. Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index
B. Clinical utility (failure rate [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up],[f] efficiency,[g] identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes)
C. Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])

Study design

1. Diagnostic test accuracy outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, and cross-sectional studies)
2. Clinical utility outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, controlled before-and-after studies, and case-control studies)
3. Safety outcomes: in addition to the above study designs, non-randomized studies without a control group (excluding non-sequential case series and case reports) will also be included

Timeframe

Publications within the last 10 years (i.e., between January 2006 and September 2016)

± = with or without; AUROC = area under the receiver operating curve; CT = computed tomography; CTV/CTA = computed tomographic angiography in combination with venous-phase imaging; DOR = diagnostic odds ratio; DVT = deep vein thrombosis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary embolism; PET-CT = positron emission tomography – computed tomography; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; V/Q = ventilation-perfusion; VTE = venous thromboembolism.

[a] Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.

[b] Leg compression US, capnography, electrocardiography, echocardiography, chest radiograph.

[c] Excluding single-detector, including CTA/CTV and triple-rule-out CT.

[d] Including planar V/Q scan, V/Q SPECT, V/Q SPECT-CT.

[e] No restriction on length of follow-up.

[f] The proportion of patients classified as having low risk of PE who receive an ultimate diagnosis of PE based on the reference standard (false-negatives/true-negatives + false-negatives).

[g] The proportion of patients in the study cohort stratified to the group with low predicted probability of PEs (sum of true and false-negatives/total cohort).