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Computed Tomography for Diagnosing Pulmonary Embolism

A Health Technology Assessment

The Health Technology Assessment Unit, University of Calgary

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Abbreviations

CDS: Clinical Decision Support

CT or CTPA: CT Pulmonary Angiography

CUS: Compressive ultrasound

DSCT: Dual Source CT

DVT: Deep vein thrombosis

ED: Emergency Department

FoV: Field of view

HTA: Health Technology Assessment

ICUR: Incremental Cost Utility Ratio

IV: Intravenous

LMWH: Low-molecular weight heparin

LUS: Lung ultrasound

mAs: milliampere seconds

MDCT: Multi-detector CT

MRI: Magnetic Resonance Imaging

PE: Pulmonary embolism

PERC: Pulmonary Embolism Rule-out Criteria

RCT: Randomized Controlled Trial

SDCT: single detector CT

SPECT: Single photon emission CT

VKE: Vitamin K antagonists

VTE: venous thromboembolism

V/Q: Ventilation Perfusion

Executive Summary

This report presents the findings and conclusions of a provincial Health Technology Assessment on the use of computed tomography (CT) for diagnosing pulmonary embolism (PE). The primary research questions were:

1) What is the appropriate use of CT to diagnose PE taking into account effectiveness, cost-effectiveness and perspectives within the BC health system?
2) If a change in use of CT is needed, what are the effective interventions to change CT use patterns?

Background: PE is the occlusion of pulmonary arterial vasculature by thrombus, tumor, air or fat. In most cases, a PE is caused by a venous thromboembolism (VTE) that forms in the leg, called a deep vein thrombosis (DVT), which breaks loose and travels through the bloodstream to the lung. Causes of thrombosis and PE are summarized by Virchow's triad: hemodynamic changes, endothelial injury/dysfunction, and hypercoagulability. Clinical data indicates that most cases of PE occur in those who are between the ages of 60 and 70; however, autopsy data show the highest incidence among individuals 70 to 80 years of age. After coronary artery disease and stroke, acute PE ranks as the third most common cardiovascular disease.

Prior to diagnostic testing, risk stratification tools may be used to determine clinical probability of PE. These tools include: Wells' Criteria, PERC and rGeneva. These tools may be used to rule out PE, but cannot be used to diagnose PE. Pulmonary angiography was historically considered to be the "gold standard" imaging test for diagnosing PE; however, other diagnostic tests, such as CT, ECG, chest x-ray, laboratory investigations (D-dimer and markers of cardiac injury and overload), ventilation-perfusion scintigraphy, MRI and/or echocardiography may be used. CT in particular has become a first-line modality for imaging in patients with suspected PE. Recent advances in CT such as helical CT, and multi-detector row CT have drastically improved the detection of small emboli, optimized contrast delivery and reduced radiation dose. Unless bleeding risk is high, anticoagulation therapy is recommended as the primary treatment for patients with a high pre-test probability of PE. Therapeutic goals for PE involve the prevention of thrombus growth, restoration of pulmonary blood flow and the prevention of recurrences

Methods: The following methodological approaches were used to gather and synthesize the available evidence:

I. Review of Clinical Practice Guidelines
II. Systematic Review on diagnostic accuracy of using CT to diagnose PE
III. Clinician interviews to determine patterns of care in British Columbia, and clinician perspectives on CT use for diagnosing PE
IV. Systematic review on patient perspectives of using CT to diagnose PE in comparison to alternatives
V. Systematic review on appropriate use of CT for diagnosing PE
VI. Cost-effectiveness model and budget impact analysis of using interventions to improve the yield of CT for diagnosing PE

Key Findings:

No Canadian or provincial guidelines exist for the diagnosis of PE. Individual centers, and in some cases individual physicians, have developed their own approaches to diagnosis. A total of 14 studies assessing the accuracy of using CT to diagnose PE were identified. All included studies were considered in the meta-analysis despite the differences in scan parameters and reference standards. The pooled sensitivity of CT for diagnosing PE is 84.8% (95% CI 81.7% to 87.5%) and the pooled specificity is 93.0% (95% CI 90.9% to 94.6%). Thus, CT is more effective at correctly identifying subjects without PE than correctly classifying patients with PE.

Emergency Department (ED) physicians working in British Columbia describe diagnosing or ruling out PE as a complex endeavour. The patient population is heterogeneous, the symptoms general in nature, and it can be challenging to determine whether a PE is clinically significant. There are societal, healthcare system and ED contextual factors that influence the PE diagnostic pathway and contribute to over-ordering of CT scans. Not diagnosing a clinically important PE may lead to death, and therefore, there is significant fear in the medical community about missing this diagnosis. Lack of access to follow-up primary care or other kinds of transitional care puts pressure on ED physicians to make a diagnosis or rule out PE before the patient leaves the ED. The physician interviews were unaware of decision support tools for diagnosing PE that

would help decrease inappropriate use of CT. Physicians felt that such a tool along with a strong strategy for physician education would be helpful although challenging to develop.

One study on patient perspectives of using CT to diagnose PE was identified. This study found that when involved in a shared decision making process, one-third of patients would decline CT testing. Reasons for declining CT testing included: risk of adverse events, and exposure to radiation from CT technology. This suggests that a shared decision making process is acceptable to patients, and that including patients in the decision on diagnostic approach may decrease imaging for PE. This study was conducted in an experimental setting, and may not be generalizable to clinical practice.

Fourteen studies were identified assessing interventions to achieve appropriate use of CT. Two studies assessed the effectiveness of an audit and feedback system, five assessed the effectiveness of a clinical decision support tool, three assessed a type of communication, three assessed the effectiveness of guidelines and one assessed both a clinical decision support tool and guideline. Pooled estimates obtained from the stratified meta-analysis demonstrate that interventions involving clinical decision support tools resulted in statistically significant increases in CT yield. Barriers such as time pressures and patient demands, as well as facilitators such as staff acceptance and buy-in, may change the success of the intervention.

A de novo cost-utility analysis was developed to evaluate the lifetime costs, health outcomes and the cost-effectiveness of interventions to promote the appropriate use of CT in diagnosing PE in emergency departments of British Columbia. In the base case, an intervention of Wells→PERC→D-dimer→CT had the lowest costs with a total of $1981 and effectiveness of 12.489 QALYs. However, the changes in effectiveness of all strategies were very small with CT resulting in only an additional 0.007 QALYs or 0.4 days of quality adjusted life. These small effectiveness increases resulted in an incremental cost utility ratio (ICUR) of $30,000 per QALY gained with Wells→D-dimer→CT (moderate and high) compared Wells→PERC→D-dimer→CT and an ICUR of $364,900 per QALY gained for CT alone compared to Wells→D-dimer→CT (moderate and high). The positive CT yield for interventions ranged from 14.2% with CT alone to 21.1% with Wells→D-dimer→CT (moderate with high).

There were very small differences in clinical effectiveness across all strategies; the difference between Wells→PERC→D-dimer→CT and CT alone is less than one additional day of life. The budget impact analysis predicts that Wells→PERC→D-dimer→CT may save up to $4 Million in the first year. Over five years, between $11.6 and $20.9 million in costs avoided may be realized for all of British Columbia for Wells→D-dimer→CT (moderate and high) and Wells→PERC → D-dimer → CT, respectively.

1 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to synthesize the evidence to support optimal use of CT (CT or CTPA) to diagnose pulmonary embolism (PE). The report summarizes evidence on the effectiveness, diagnostic accuracy, cost-effectiveness, and patient experience of using CT to diagnose PE. In addition, this report includes a synthesis of interventions to achieve optimal use of CT for the diagnosis of PE. A cost-effectiveness and budget impact of the effective interventions is also reported.

2 Research Question and Research Objectives

The primary questions are:

- What is the appropriate use of CT to diagnose PE taking into account effectiveness, cost-effectiveness and perspectives within the BC health system?
- If a change in use of CT is needed, what are the effective interventions to change CT use patterns?

The primary research objectives are:

- To determine the effectiveness/efficacy of CT for diagnosing PE
- To determine the diagnostic accuracy of CT for diagnosing PE
- To determine patient's perspectives on the use of CT for diagnosing PE
- To identify and determine the effectiveness of interventions to support appropriate use of CT for diagnosing PE
- To determine the cost effectiveness and budget impact of using interventions to improve the yield of CT for diagnosing PE

3 Background

3.1 Pulmonary Embolism Overview

Pulmonary embolism (PE) is the occlusion of pulmonary arterial vasculature by thrombus, tumor, air or fat. In most cases, a PE is caused by a venous thromboembolism (VTE) that forms in the leg, called a deep vein thrombosis (DVT), which breaks loose and travels through the bloodstream to the lung.[1] Deep vein thrombosis, and subsequent PE, often results from the body being stationary for long periods of time.[2] Although thrombi most commonly originate in the leg, they may also originate in the pelvic, renal or upper extremity veins, or in the right heart chambers.[2] Without intervention, approximately 50% of people with proximal DVT develop PE as the freed blood clot enters the lungs.[3]

PE can either be acute or chronic.[2] In acute cases, symptoms develop immediately after occlusion of pulmonary vessels, whereas in chronic cases patients tend to develop slowly progressing dyspnea over a period of time, sometimes years [2]. Causes of thrombosis and PE are summarized by Virchow's triad: hemodynamic changes, endothelial injury/dysfunction, and hypercoagulability. However, PE can also be found in 20% of patients without predisposing factors.[4] PE can lead to hypoxemia, permanent damage to the affected lung, and/or damage to other organs receiving limited oxygen.[1] Without treatment, approximately 30% of patients with PE will die in the first 3 months.[5] This mortality rate can be significantly decreased with treatment, which helps restore blood flow and prevents additional blood clots from forming.[1]

PE symptoms include shortness of breath, chest pain, or hemoptysis.[1] Other common symptoms are fever, hypotension, cyanosis, pulmonary hypertension, syncope and heart palpitations.[6,7] However, approximately half of all cases remain asymptomatic.[8] In many cases, death due to acute PE is a result of acute right heart failure.[9] However, it is important to note that symptoms are non-specific; thus the diagnosis of PE is often missed or delayed, and in some instances an autopsy is the only identifier of PE as the cause of death.[10]

3.2 Prevalence and Incidence

The true incidence of PE remains unknown due to the asymptomatic nature of the disease.[2] In British Columbia, an average of 3,551 patients were diagnosed with PE annually between 2012

and 2015. Of the patients diagnosed in 2014/2015, 77% had a CT scan. In a 2001 study of emergency departments in four tertiary hospitals in Canada, 86 of 930 patients suspected of PE were diagnosed with PE[11]. This suggests the prevalence of PE among those patients suspected of PE is 9.25%[11]. Clinical data indicates that most cases of PE occur in those who are between the ages of 60 and 70; however, autopsy data show the highest incidence among individuals 70 to 80 years of age.[5] British Columbia specific data suggests that in 2014/2015 the average age of diagnosis was 64.63, with the highest rate of diagnosis in those who are 80 years and older. After coronary artery disease and stroke, acute PE ranks as the third most common cardiovascular disease.[5]

3.3 Disease Progression and Severity

If left untreated, acute PE is associated with a mortality rate as high as 30%, whereas the death rate of treated PE is 8%.[5] PE generally occurs 3-7 days after the onset of DVT.[12] British Columbia specific data provided by the BC Ministry of Health suggests that 7 days after diagnosis, 1.93% of patients have died, and 24.01% have died one year after diagnosis. However, published studies suggest this might be high; Pengo et al. found 13.4% had died after one year.[13] Typically, the course of events will follow from one of the following two cases of PE:

1. Small to medium embolus: artery blockage will cut off circulation from a part of the lung, and shortness of breath will occur. In 10% of these cases, the region of the lung supplied by the blocked artery will die due to inadequate blood flow.[3] This region will eventually heal with a fibrous scar.[3]
2. Massive embolus: may lodge in the main pulmonary artery, which will occlude nearly all blood flow to the lungs. The right side of the heart will experience back-pressure, which will reduce the amount of blood pumped from the heart to the lungs, and cause heart failure.[3] This may occur suddenly (due to a massive PE) or gradually (due to recurrent PE).[14] Patients presenting with a massive PE will experience severe bradycardia (heart rate <40 beats per minute), shock and have a high risk for short-term mortality.[3]

Along with mortality, PE can often precede recurrent venous thromboembolism and long-term health issues.

Recurrent venous thromboembolism may occur during anticoagulant treatment or following the resumption of anticoagulant treatment.[15] The risk of long-term recurrent VTE in patients with PE has been assessed in multiple randomized controlled trials.[16-20] Those not treated with long-term anticoagulant therapy for three-months after PE had a statistically significant higher risk of recurrent VTE compared to those on anticoagulant therapy.[16-20]

Additionally, multiple studies have reported that a significant proportion of patients are at high risk of developing persistent perfusion defects after a PE.[21,22] These patients were more likely to report dyspnea on exercise, and have a higher pulmonary artery pressure at follow-up.[21] However, additional studies are required to determine the long-term significance of these persistent defects.[15,21]

PE may increase risks for other diseases. It is well established that patients with acute PE have a higher risk of cancer and arterial cardiovascular events than population controls.[23,24]

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease that has also been estimated in several cohort studies following an episode of PE. In one study the cumulative rate of symptomatic CTEPH was 3.8% (95% CI, 1.1-6.5) 2 years after a first episode of acute PE.[25] However, a higher level of data is required to confirm the true occurrence of CTEPH after an episode of acute PE.[15]

3.4 Risk Factors

PE develops in about half of cases with confirmed DVT thus risk factors for DVT are also considered risk factors for PE.[2] See Table 1 for a summary of predisposing factors for PE.

Table 1: Inherited or acquired Predisposing factors for PE [9]

Strong predisposing factors (odds ratio >10)	Moderate predisposing factors (odds ratio 2–9)	Weak predisposing factors (odds ratio <2)
Bone fractures (hip, leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Immobility due to sitting (e.g., prolonged car or plane travel)
Major general surgery	Chemotherapy	Increasing age
Major trauma	Chronic heart or respiratory failure	Laparoscopic surgery (e.g., cholecystectomy)
Spinal cord injury	Hormone replacement therapy	Obesity
	Malignancy	Pregnancy (antepartum)
	Oral contraceptive therapy	Chronic venous insufficiency, varicose veins
	Immobility after stroke	
	Pregnancy (peripartum)—Lactation	
	Previous venous thromboembolism	
	Thrombophilia	

3.5 Diagnosis

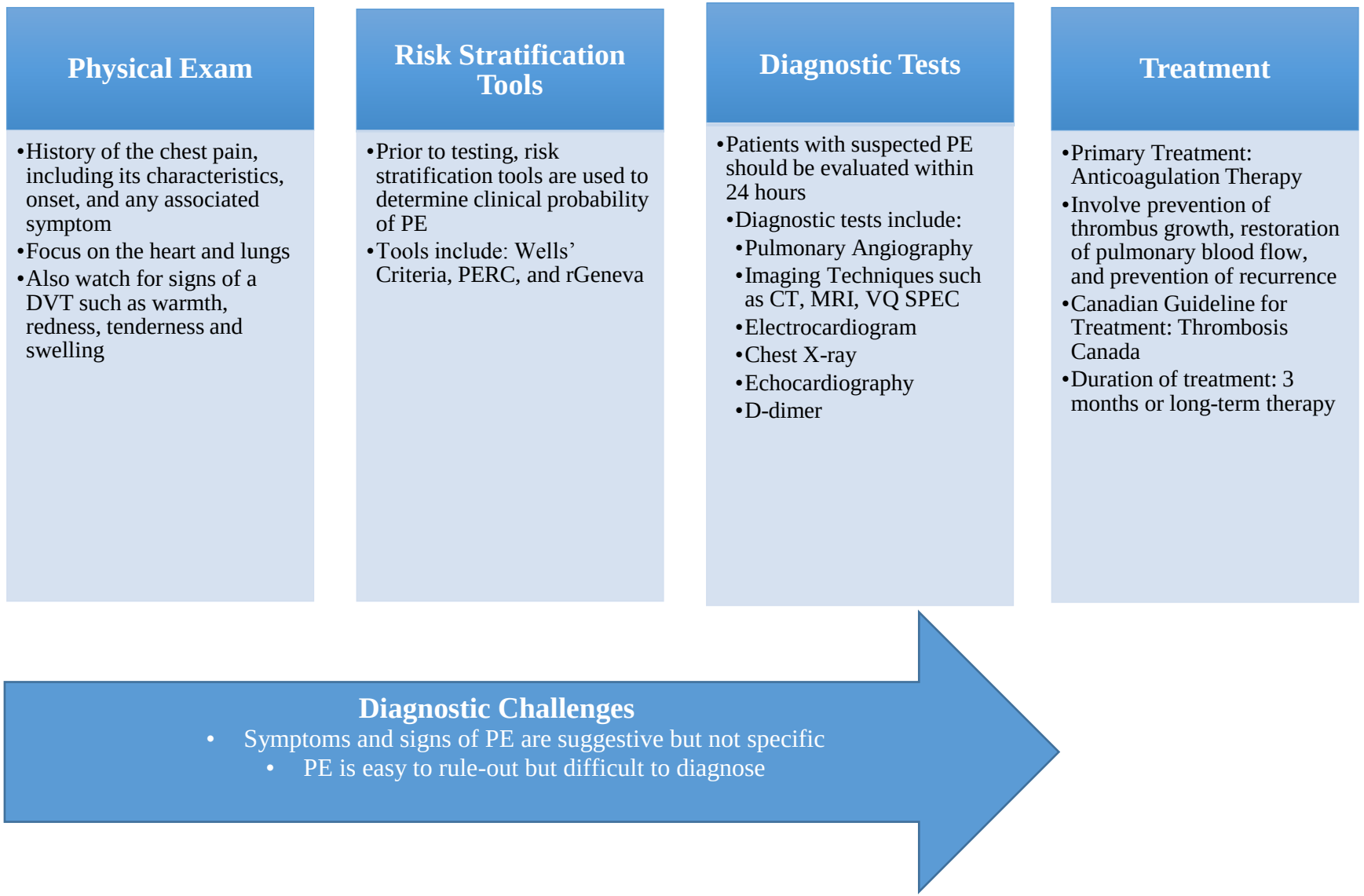
PE can be difficult to diagnose, especially if the patient has underlying lung or heart disease.[26] PE may be diagnosed using validated prediction rules, ECG, laboratory investigations (primarily D-dimers and markers of cardiac injury and overload), imaging techniques (most commonly CT, ventilation-perfusion scintigraphy and x-ray) and/or echocardiography.[5]

The elements related to diagnosing PE will be outlined in the following sections, including, physical exam, risk stratification tools, diagnostic tests, diagnostic challenges and treatment (Figure 1).

Physical Exam

The healthcare professional will take a history of the chest pain, including its characteristics, its onset, and any associated symptoms that may direct the diagnosis to PE. Physical examination will concentrate on the heart and lungs, as shortness of breath and chest pain have a broad range of differential diagnoses.[27] Physical examination may include assessment of DVT signs and symptoms, including warmth, redness, tenderness and swelling. It is critical to account for risk factors for clotting, because signs associated with DVT may be completely absent in the presence of a clot.[27]

Figure 1: Diagnosis Overview



3.6 Risk Stratification

Suspected or confirmed PE patients are stratified into high, intermediate, or low risk based on their risk for short-term mortality.[28] High-risk patients are identified by the presence of hypotension, respiratory failure, or shock.[9] These characteristics of hemodynamic stability should be assessed during the acute phase in the hospital to enable evaluation of the likely risk of patient mortality due to PE.[9] Risk stratification is not straightforward as some patients who present as normotensive are still at an increased mortality risk.

3.6.1 Risk Stratification Tools: Wells, rGeneva, and PERC

Explicit clinical prediction rules supplement implicit clinical judgement. Validated clinical prediction tools include the Wells' Criteria, the revised Geneva score, and the Pulmonary Embolism Rule out Criteria (PERC). These can aid clinicians in stratifying patients into low, intermediate, or high probability groups, or into "PE likely" and "PE unlikely" groups.[29]

3.6.2 Wells' Criteria

The Wells' Criteria for PE quantifies the risk of PE and provides an estimated pre-test probability.[30] The Wells Criteria uses seven criteria to assess the possibility of a PE (Table 2). Each criteria is associated with a certain number of points, with evidence of DVT having the most points, and therefore the highest weighting, and hemoptysis (coughing up blood) and malignancy associated with the lowest number of points [31]. All points are summed to provide a probability of having PE, with a maximum total of 12.5 points. Scores are interpreted based on three tiers; low probability is less than two points, moderate probability is 2-6 points, and high probability is greater than 6 points [31].

Table 2: Wells Criteria Tool[31]

Clinical Signs and Symptoms of PE	**Points***
Evidence of DVT (leg swelling, pain with palpation)	3
Heart rate higher than 100 beats per minute	1.5
Previous objectively diagnosed DVT or PE	1.5
Immobilization for three or more consecutive days or surgery in the previous four weeks	1.5
Hemoptysis	1
Malignancy	1
PE as a highly likely diagnosis	3

*Probability of PE: <2 points=low, 2-6 points=moderate, >6 points=high

A simplified Wells' criteria has also been developed [29]. The simplified Wells scoring system replaces the weighted scores for each criteria with a 1 point score for all present symptoms and clinical signs [29]. The total score is summed, with a highest possible score of 7 points. Using the simplified Wells' Criteria, a score less or equal to 1 is considered unlikely, and a score of greater than 1 is considered likely [29].

The weighted and simplified Wells' Criteria have been validated in both inpatient and emergency department settings. They are simple to use and provide straightforward cutoffs for the predicted probability of PE. Although Wells' has received some criticism for its involvement of more "subjective" criterion, Wells' also has the potential to reduce the number of CT scans performed on low-risk PE patients.[30] It is also important to note that: 1) Wells' should only be used in patients with a clinical suspicion for PE, and 2) Wells' does not diagnose PE but rather Wells is a risk stratification tool identifying pre-test probability and to guide appropriate further testing. [32,33]

3.6.3 rGeneva Score (Revised Geneva Score)

Similar to the Wells Score, the Revised Geneva Score provides a tool to quantify the risk of PE. The rGeneva Score is often the preferred score due to its objectivity [34]. The original Geneva

score was criticized for its inclusion of both a Chest X-ray and arterial blood gas to be applied; the revised score does not include these.

The rGeneva score uses nine variables to identify PE risk. As with the Wells' Criteria, these variable are weighted using points; having a heart rate over 95 beats per minute is given the most weight, with 5 points assigned [34]. A total of 17 points may be assigned, plus an additional 4 points if the heart rate is between 75-94 beats per minute or an additional 5 points if the heart rate is above 95 beats per minute. Based on these scores, the rGeneva stratifies patients in to low, intermediate or high risk; 0-3 points indicates low probability of PE, 4-10 points indicates intermediate probability, and 11 or more points indicates high probability [34].

By identifying low risk patients, the rGeneva score provides assistance in decreasing the number of unnecessary imaging tests performed for PE.[34] Similar to the Wells score, the rGeneva is not meant to diagnose PE but rather to guide workup and testing by predicting pre-test probability of PE.[34]

Table 3: Revised Geneva Score Tool [34]

Variable	**Score**
Age 65 or older	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75-94 beats per minute	3
Heart rate 95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral edema	4

*0-3 points indicates low probability, 4-10 points indicates intermediate probability, 11 or more points indicates high probability

As with the Wells' tool, there is also a simplified version of the Revised Geneva Tool [29]. The simplified Geneva Tool replaces the weighted scores for each criteria with a 1 point score for all

variables, with the exception of having a heart rate over 95 beats per minute, which receives 2 points [29]. The total score is summed, with a highest possible score of 10 points. Using the simplified Geneva Tool, a score of 2 or less is considered unlikely to have PE[29].

3.6.4 Pulmonary Embolism Rule-out Criteria (PERC)

The PERC rule can be applied to patients with a low-risk of PE but where PE diagnosis is being considered.[35] Using a series of 8 questions, PERC allows a physician to evaluate the risk of PE. PERC is a "rule-out" tool; if the answer to all eight questions is "no," no testing is required.[35] It is also a unidirectional test; while PERC negative allows for the avoidance of further testing, PERC positive does not necessarily lead the clinician to order further tests.[35]

Figure 2: Pulmonary Embolism Rule-out (PERC)

Pulmonary Embolism Rule-Out Criteria
• Is the patient >49 years of age? • Is the pulse rate >99 beats per minute? • Is the pulse oximetry reading <95% while the patient breathes room air? • Is there are present history of hemoptysis? • Is the patient receiving exogenous estrogen? • Does the patient have a prior diagnosis of venous thromboembolism? • Has the patient had recent surgery or trauma requiring endotracheal intubation or hospitalization in the previous 4 weeks? • Does the patient have unilateral leg swelling?

*If the answer to all questions is "no," then diagnostic testing is not necessary

In the case of a low-risk patient who is not PERC negative, the physician should consider d-dimer for further evaluation.[35] If this d-dimer is negative and pre-test probability is <15%, the patient may not require further testing for PE.[35] If the d-dimer is positive, further testing such as CT-angiography or V/Q scan is warranted.[35] It is important to note that PERC should not be utilized for patients with moderate or high risk of PE. In these cases d-dimer or imaging testing is required.[35]

3.7 Diagnostic Tests for PE

There is yet to be developed a single noninvasive test for PE that has achieved perfect specificity and sensitivity as well as minimized risk, although attempts to optimize the value of history and

physical examination are continuous.[7,36] Often, a combination of CT and one or more additional tests are used. Four non-CT tests (d-dimer, V/Q scanning, leg ultrasound and MRI scanning) are commonly used to diagnose PE. Some of these tests, such as d-dimer, are primarily only adequate for ruling out PE, while others such as ventilation–perfusion (V/Q) lung scanning, have the ability to both rule out and diagnose PE.[37]

3.7.1 Pulmonary Angiography

An angiogram is an X-ray test that uses iodine dye and a camera (fluoroscopy) to take images of the blood flow in an artery or a vein.[38] A pulmonary angiogram is defined as an angiogram of the blood vessels of the lungs.[39] During the test, a catheter (thin tube) is placed in a blood vessel in either the groin or just above the elbow, and subsequently guided towards the lungs.[38] The iodine dye (contrast material) is then injected into a vessel; this dye and the use of fluoroscopic x-rays allow the healthcare professional to clearly see the vessels that send blood to and from the lungs.[38,39] Diagnostic criteria for acute PE in direct angiography involve direct evidence of a thrombus, either a filling defect or amputation of a pulmonary artery branch.[40]

From the late 1960s onwards, pulmonary angiography had been considered the "gold standard" imaging test for diagnosing PE.[40,41] Direct angiography allows for the visualization of thrombi as small as 1-2 mm within subsegmental arteries.[42] However, this test is invasive and did not avoid exposing the patients to hazards, including a slight mortality risk.[43] The risks and costs associated with pulmonary angiography and the availability of alternatives have warranted an increase in the use of non-invasive diagnostic approaches for PE. The more recent development of new, non-invasive diagnostic techniques such as CT in the 1990s have decreased the role that direct pulmonary angiography plays in the diagnosis of PE; it is now rarely used as a sole diagnostic procedure.[40]

3.7.2 D-dimer

D-dimer forms in the body when cross-linked fibrin is lysed (dissolved or destroyed) by plasmin.[37] It reflects the ongoing activation of the hemostatic system.[37,44] D-dimer testing involves the conduction of a blood test to measure a substance that is released after a blood clot breaks up.[45] A low or normal d-dimer test result indicates that only a minor amount of the

substance released as the clot breaks up; thus, problems resulting from this blood clot are not likely. A higher than normal d-dimer level signals the potential for a blood clot issue to develop; d-dimer levels are often higher than normal in patients with abnormal blood clotting.[45] Elevations of D-dimer are non-specific; for instance, D-dimer is increased by aging, inflammation or cancer, and thus an abnormal result has a low positive predictive value. With respect to the role of d-dimer testing in the diagnosis of PE, a negative D-dimer result can assist in the exclusion of PE. The clinical probability estimate, determined by information from the patient's history and physical examination, can be assessed by either a formal numerical model,[30,46] or an informed intuitive estimate.[47,48]

D-dimer testing as an assistant in the diagnosis of PE can be divided between two types of D-dimer assays, very highly sensitive and moderate-to-highly sensitive. Very highly sensitive D-dimer assays[1] have a sensitivity for PE of around 98% or higher.[37] The high negative likelihood ratio of these assays is sufficient to rule out PE in all patients; thus these assays may be considered a "standalone" test for the exclusion of PE.[49] Moderate to highly sensitive D-dimer tests have a sensitivity for PE of around 85%-98%.[37] Because the negative likelihood ratio and predictive value of these tests are not high enough to rule out PE in consecutive patients, a normal result must be combined with an additional assessment which classifies patients as having a lower pretest probability for PE. European Society of Cardiology guidelines state that in 32-40% of patients with low to intermediate pretest clinical probability and normal D-dimer levels, PE can be safely excluded without further testing.[50]

3.7.3 Ventilation/Perfusion (V/Q) Scanning

A lung V/Q scan is an imaging test that involves two nuclear scan tests to measure breathing (ventilation) and circulation (perfusion) in all areas of the lungs.[51] These tests may be done separately or together.[51] The ventilation scan measures air flow into the lungs;[52] the patient will breathe in radioactive gas through a mask while sitting or lying under the scanner arm.[51] The perfusion scan observes where blood flows in the lungs;[52] a radioactive albumin is injected into

[1] * Assay: investigative (analytic) procedure in laboratory medicine, pharmacology, environmental biology and molecular biology for qualitatively assessing or quantitatively measuring the presence, amount, or functional activity of a target entity

the patient's vein, and then the scanner observes the lungs as blood flows through them to find the location of the radioactive particles.[51] Although there is a slight exposure to radiation from the radioisotope, no radiation is released from the scanners; rather they detect radiation and convert it into an image.[51] The healthcare professional then evaluates the ventilation scan and the perfusion scan with a chest x-ray.[51] Results that show the lungs taking up lower than normal amounts of radioisotope during either of the scans may be indicative of a pulmonary embolus.[51]

A normal perfusion scan can exclude PE,[53] although only around 25% of patients have a normal perfusion scan.[46] Perfusion defects are nonspecific, and PE is found in a third of patients with perfusion defects. However, the probability that PE is causing perfusion defects will increase with increasing size and number of defects, as well as the presence of a normal ventilation scan and features of perfusion defects such as a wedge-shaped area in the lung periphery. [37,47,54] The V/Q test is based principally on an intravenous injection of macroaggregated albumin particles, which block a small fraction of pulmonary capillaries and thus allow for scintigraphic assessment of lung perfusion at the tissue level.[55] Perfusion scans are combined with ventilation studies for the purpose of increasing specificity. Lung scan results assisting in the diagnosis of PE are typically classified into four categories depending on criteria established in the North American PIOPED trial: normal or near-normal, low, intermediate (non-diagnostic), and high probability of PE.[56] Numerous clinical outcome studies evaluating the validity of a normal perfusion lung scan have concluded that it is a safe practice to withhold anticoagulant therapy in patients with a normal perfusion lung scan.[57,58]

A 2014 systematic review and meta-analysis assessing the accuracy of V/Q SPECT in the diagnosis of PE found that the sensitivity and specificity of this technology using a per-patient-based analysis was 96% (95% CI: 95-97%) and 97% (95% CI: 96-98%)[59]. The area under the receiver operator curve was 0.99 in this per-patient-based analysis[59]. The authors of this study conclude that V/Q SPECT is an accurate method of diagnosing PE with a high sensitivity and specificity[59].

3.7.4 Magnetic Resonance Imaging (MRI)

MRI scanning employs radio frequency waves and a powerful magnetic field to produce detailed images of internal structures.[60] While MRI scans have been used to observe areas of the body for some decades, MRI for the chest has developed relatively recently.[61] Several challenges that had previously impeded its use included the motion of both heart and lungs, the lack of protons within the chest, poor contrast between flowing blood and an embolus, and susceptibility artifacts resulting from the interfaces between air and soft tissues.[61-65] However, novel sequencing, combined with increased gradient-strength systems, facilitated the advent of lung perfusion MRI, direct thrombus imaging of the entire venous system, and the introduction of hyperpolarized 3-helium, allowing high-resolution lung ventilation imaging. The development of faster magnetic resonance hardware, combined with a dynamic gadolinium enhancement of contrast dye, has made high-resolution angiography possible during a single suspended breath.[66] This new three-dimensional magnetic resonance angiography during a single breath hold can be used as a safe, fast and accurate assistive imaging technique for the diagnosis of PE.[66] Today, a wide range of MRI techniques may be applied for diagnosis of VTD and PE.[61] MRI is a relatively costly technology and thus is often reserved for pregnant women to avoid radiation to the fetus, and for patients whose kidneys may be harmed by dyes used by other tests.[60] Nonetheless, current MRI technology exhibits a high specificity and sensitivity for proximal PE, and a positive result may aid in clinical decision making.[67] MRI's inherent lack of ionizing radiation has been underscored both in general use of MRI to diagnose PE, and in pregnant patients.[68,69]

A systematic review and meta-analysis by Zhou et al. assessed the accuracy of MRI for the diagnosis of PE[70]. Based on fifteen studies, this study found an overall sensitivity and specificity of 0.75 (95% CI: 0.70-0.79) and 0.84 (95% CI: 0.80-0.87) using a patient-based analysis[70]. The authors concluded that MRI yielded high diagnostic accuracy, but that motion artifact and poor arterial opacification resulted in inconclusive MRI exams in 18.89% of the participants[70].

3.7.5 Lung Ultrasound (LUS)

Since its emergence approximately 15 years ago,[71] lung ultrasound technology has been increasingly used to complement conventional assessment methods and other imaging modalities of the lung in the diagnosis of PE.[72] Traditionally used to assess pleural effusions and masses,

LUS has been revolutionized to image the pulmonary parenchyma, primarily as a point-of-care technique.[71] In general, the ultrasound imaging process has significant differences from radiographic imaging in which x-ray beams are used. LUS can be performed in any position and on the entire chest, laying the probe in the intercostal spaces and avoiding the ribs.[71] The probe is placed both longitudinally, perpendicular to the ribs, and obliquely along the intercostal spaces.[71] Ultrasound machines are lightweight, compact, easy to transport and robust, thus allowing multiple bedside examinations.[73] LUS is also not only easily available at bedside but, similar to MRI scans, can be performed with the absence of an ionizing radiation risk.[73] In addition to lower limb compressive venous ultrasonography and echocardiography, lung ultrasound can play an important role in the diagnosis of PE in selected patients' subgroups.[74] It can be safely used under conditions of both pregnancy and renal insufficiency, and can be highly useful as a bedside test for hemodynamically unstable patients.[74] LUS provides accessibility to only two-thirds of the lung area and thus more central lesions may potentially be missed.[74] A 2013 systematic review of studies involving a total of 887 patients and evaluating the diagnostic accuracy of LUS for the diagnosis of PE found bivariate weighted mean sensitivity to be 87.0% (95% CI 79.5, 92.0%), and bivariate weighted mean specificity was 81.5% (95% CI 71.0, 89.3%).[75] However, not all hospitals have access to fulltime LUS and many emergency physicians lack the skills to perform and interpret this technically difficult exam on their own.

3.7.6 Echocardiogram

An echocardiogram is a sonogram of the heart. Information from Doppler ultrasound, B-mode ultrasound, and M-mode ultrasound are combined to create images of the heart. These images provide information about the size of the heart, the function of the valves, and the strength of the heart muscle. The echocardiogram is used to identify areas of the heart that are not working well. When patients with a PE have an echocardiogram, approximately 40 percent will be found to have abnormalities of the right side of the heart, particularly the right ventricle. While an echocardiogram is not actually used to diagnose a PE, it can identify strain on the right side of the heart caused by a large PE as well as certain heart problems that may imitate a PE.

3.8 Computed tomography (CT) Overview

A technology that has revolutionized diagnostic radiology,[76] CT is defined as a form of radiography in which a three-dimensional image of a body structure is constructed by computer from a series of plane cross-sectional images made along an axis.[77] The CT scanner sends X-rays through the body, with each rotation of the scanner producing images of a thin slice of the area.

Clinicians using conventional CT were subject to various limitations such as poor x-axis resolution, a scan plane resolution of only ~1-2 lp/mm, section-to-section misregistration due to variations in patient respiratory motion.[78] Conventional CT also resulted in an inter-scan delay from the stop-start actions of table translation and cable unwinding.[78] Yet since its invention in 1972, CT has evolved significantly. The first two major leaps in the evolution of CT were spiral or helical CT in the early 1990s, and multiple-row detector CT in the late 1990s to 2000s.[78]

The categorization of CT use is based on the population of patients (adult or pediatric) and the purpose of imaging (either diagnosis in symptomatic patients or screening of asymptomatic patients).[76] Although diagnosis using CT is most often used for adults, CT use has increased pediatric diagnosis and adult screening; a trend that is expected to continue.[76]

3.8.1 Types of CT

3.8.1.1 Single detector CT (SDCT)

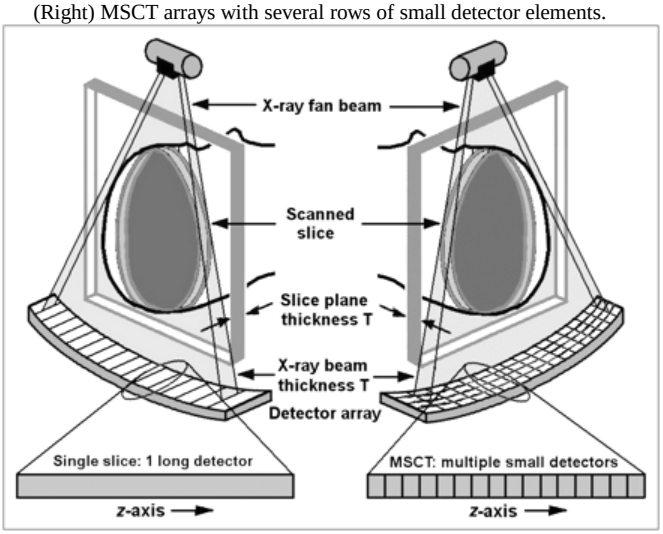
The primary characteristic of SDCT hardware is denoted by its composition of a one-dimensional set of detector arrays.[79] SDCT capabilities include the elimination of inter-scan delay, large tissue volumes scanned in short times, and improved Z axis resolution by over-sampling.[78] The SDCT also permits over-sampling without an increased dose of radiation. However, single slice CT has various limitations including poor utilization of the X-ray tube, it is only capable of near isotropic resolution over small volumes, and large volume scans in short durations are limited.[78]

3.8.1.2 Multi Detector CT (MDCT)

The most significant difference between single-slice CT and MSCT hardware lies in the design of the detector arrays.[79] The linear array of elements used in conventional and helical CT scans was replaced; in MDCT, each of the individual, SSCT detector elements in the z-direction is

divided into many smaller detector elements.[79] This forms a two-dimensional array of detector elements with anywhere between 4-64 rows.[80] MDCT allows for CT scanners to acquire multiple slices or sections simultaneously (in one rotation), for increased resolution. MDCT allows for a significant increase in the speed of CT image acquisition, and also involves a more complex image reconstruction compared to single section CT. [80] The introduction of multidetector over single-detector techniques has increased the number of subsegmental (presence of PE on subsegmental level only) PE diagnoses.[81] It has also lead to the subsequent development of higher-resolution CT imaging such as CT angiography.[81]

Figure 3:[79] (Left) SSCT arrays containing single, long elements along z-axis. (Right) MSCT arrays with several rows of small detector elements.



3.8.1.3 Dual Source CT (DSCT)

In contrast to a conventional multislice CT which uses a single X-ray generator, Dual source CT is equipped with two X-ray tubes, each with different energy levels.[82] Two corresponding detectors with an angular offset of 90 degrees are oriented in the gantry. Thus, DSCT is characterized by its two different operating modes: two X-ray sources and two detectors, used at the same time in different scanning modes.[82] This setup allows for a higher level of information/resolution to be obtained, while reducing the radiation dose by up to 50% as compared to a single source CT.[82] However, currently DSCT provides no significant additional benefit for diagnosing PE, and the full range of applications of novel Dual Energy information is still under clinical investigation.[82]

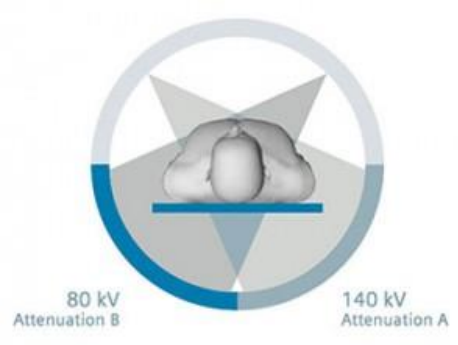


Figure 4:[82] Dual Source CT equipped with two X-ray tubes. Courtesy of: Siemens AG

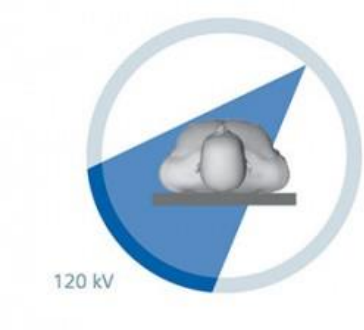


Figure 5:[82] Conventional multislice CT with one X-ray generator. Courtesy of: Siemens AG

3.8.1.4 Helical (Spiral) CT

Helical CT was introduced in the early 1990s and is characterized by its fast speed and continued volumetric acquisition as the patient moves through the gantry.[83] Complete helical CT exams can be performed in under five minutes,[84] with the scan's ability to image the entire lung during a single breath-hold and the associated decrease in image misregistration.[85] Besides shortened examination time, helical CT has improved visibility of vascular structures, the capability for retrospective imaging and three dimensional vascular studies, and potential reduction in the required amount of contrast material.[83] These scanners are also equipped with multiple parallel detector arrays, which acquire a higher level of data per scan rotation and as well as added data to display unique representations of intrathoracic structures.[83]

Yet even these advances in CT technology have not avoided potential pitfalls. Even with its improved visibility, the use of spiral CT has limitations in terms of the accurate diagnosis of small peripheral emboli.[86] Moreover, although it is noninvasive spiral CT use is still associated with radiation exposure risk.[86]

3.8.1.5 Single Photon Emission CT (SPECT)

SPECT involves the fusing or merging of images from two different types of scans taken; a CT scan and a radioactive material (tracer). The tracer allows the clinician to observe blood flowing to tissues and organs.[87] Centres for nuclear medicine are increasingly using SPECT techniques over the planar technique for diagnosing PE; SPECT technology has been proven to have fewer indeterminate results and a higher diagnostic value.[55] One of the most current advances is a

combination of a low-dose CT scan with a Ventiliation/Perfusion (V/P) SPECT scan in a hybrid tomograph.[55]

3.8.2 CT Scan Parameters[2]

Different types of CTs use different scan parameters, such as tube potential, tube current, scan time, collimation and helical pitch (Table 4). There are also different reconstruction parameters which specify how the image is viewed (Table 4). Studies that use CT often report the scan and reconstruction parameters to provide the necessary details to replicate the results.

Table 4: CT Scan Parameters

Scan Acquisition Parameters	Tube Potential	The electric potential applied across an x-ray tube to accelerate electrons towards a target material. Expressed in units of kilovolts. For CT, generally (80-140 kV) voltage between cathode and anode. Scanner feature- depends on brand and detector type (single or multi).[88]
	Tube Current	The number of electrons accelerated across an x-ray tube per unit time. Expressed in units of milliampere (mA). (20-500 mA) current flowing through filament. Scanner feature- depends on brand and detector type (single or multi).[88]
	Tube current-time product	The product of tube current and exposure time per rotation, expressed in units of milliampere seconds (mAs). A. In axial scan mode, this is equal to: tube current * (scan angle / 360) * rotation time B. In helical scan mode, this is equal to: tube current * rotation time.[88]
	Scan time	CT scanners have the ability to acquire data for a slice typically between 0.5-4 seconds.[89]
	Collimation/slice width	The number of slices. The smaller the slice width (ranging from 0.5-10mm), the higher the scan time.[88]
	Helical pitch	A unit-less parameter used to describe the table during helical CT; equal to table travel (mm) per gantry rotation divided by total nominal beam width (mm) (0.5-3)- higher the pitch, more area that covers.[88]
Reconstruction Parameters	Field of view (FoV) (10-50 cm)	Width of the square region mapped to the reconstructed image matrix. Scan area. A smaller FoV provides better resolution.[88]
	Reconstruction	A matrix of small boxes of tissue called voxels, each with attenuation coefficient, that forms the scanned

[2]A comprehensive overview of the principles of CT technology within the evolutionary context of CT can be found in "Principles of CT and CT Technology" by Lee W. Goldman.

	Matrix	slice.[90] If a 512 x 512 matrix is used (as is common today), each voxel is approximately 0.5 x 0.5 mm.[90] X-Ray transmission measurements (Ni) can be expressed as the sum of attenuation values occurring in voxels along the pay of ray for Ni.[90] As such, the objective of CT image reconstruction is to determine how much attenuation of the narrow x-ray beam occurs in each voxel of the reconstruction matrix.[90]
	Reconstruction Filter	A scan data processing method that defines the quality of view by determining sharpness or smoothness of the image in the axial plane.[88]
	Reconstruction Interval	The distance between two consecutive reconstructed images (i.e. 1.25 mm). Alters the view and quality, and has a thinning property.[88]

Using CT to Diagnose PE

As a fast and non-invasive technology, CT is often one of the first-line modalities for imaging of pulmonary circulation in patients with suspected PE.[81] CT can also reveal the extent of the PE, identify signs of right ventricular dysfunction, as well as provide alternative diagnoses.[50 9]

CT acquires images of the lung using a breath hold technique during the pulmonary arterial enhancement phase following the injection of intravenous contrast material. Similar to observations discovered through means of pulmonary angiography, the PE would appear as a filling defect in the pulmonary artery as it becomes more opaque from the contrast. Further advances in CT technology such as multidetector rows have allowed for a highly refined and detailed evaluation of the entire pulmonary vascular tree, and significant improvements in the detection of peripheral PE. Due to its noninvasive nature as well as its sensitivity and specificity, CT is currently considered the first line imaging tool for the evaluation of suspected PE.

CT use for diagnosis of PE is increasing at a rapid pace due to large advances in technology that make CT user friendly for both the physician and patient.[76] However, compared to conventional x-ray imaging procedures, CT exposes patients to higher doses of radiation. CT 16-array or greater delivers a higher absorbed dose (8-20 mSv[3]) to breast tissue than conventional V/Q

[3] mSv- radiation dosimetry. The average accumulated background radiation dose to an individual for 1 year, exclusive of radon, in the United States.

imaging (0.6-3 mSv).[91] These differences reflect variations in size and configuration of breast tissue, CT parameter settings, and the methods used to measure radiation dose.[91] Risk associated with radiation exposure also depends on patients' age; patients above 40 years have lower risk due to the relatively lower life expectancy after this age, and the latency period of tumors induced by radiation.[76,81,92] Although data on the carcinogenic potential at relatively low dose CT imaging are lacking, the excess stochastic risk of fatal cancer induction in a standard person undergoing CT with the current effective dose of 3-6 mSv is 15-30 excess deaths per 100,000 persons.[93,94]

Various developments in CT imaging such as helical/spiral CT have enhanced the detection of small emboli as well as visuals of peripheral pulmonary arteries.[95] New technologies such as multi-detector row CT have also allowed for improvements towards optimizing contrast material delivery, and reducing radiation dose.[95]

3.9 Treatment

Unless bleeding risk is high, anticoagulation therapy is recommended as the primary treatment for patients with a high pre-test probability of PE.[96,97] If administered promptly, anticoagulation is effective at preventing a thrombus from extending proximally and at decreasing mortality and morbidity associated with PE.[98] Therapeutic goals for PE depend on the severity but typically involve the prevention of thrombus growth, restoration of pulmonary blood flow and the prevention of recurrences.[9]

Thrombosis Canada has developed a comprehensive set of guidelines for the treatment of PE in Canada.[97] In patients with intermediate and low pre-test probabilities of PE, treatment may be withheld under the condition that definitive diagnostic testing will be completed within 4 hours (intermediate pre-test probability) or 24 hours (low pre-test probability). Patients with a high pre-test probability of PE should be treated with anticoagulation therapy. All patients with a confirmed PE diagnosis should be risk-stratified to determine whether outpatient management will be sufficient or if in-hospital treatment is required. If a patient presents with hypotension that is due to a cause such as tachycardia or sepsis, or is not responsive to a small fluid challenge, risk of early mortality lies at 15% and thus the patient should be admitted and considered for

thrombolytic therapy.[97] PE-confirmed patients who are clinically well and present with no evidence of right ventricular dysfunction or myocardial injury have a significantly lower mortality risk (<1%) and thus home treatment or early discharge may be appropriate.[97] Recommendations for duration of treatment are below in Table 5.

Table 5: Thrombosis Canada, Recommendations for Duration of Treatment of PE or DVT

Categories of VTE	Duration of Treatment
Provoked by a transient risk factor*	3 months
First unprovoked† VTE	Minimum of 3 months and then reassess
Proximal DVT or PE with no or only minor risk factors for bleeding	Long-term therapy with annual review
Isolated distal DVT	3 months‡
Second unprovoked VTE	Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review¶
Cancer-associated VTE	Minimum of 3 months and then reassess. Continue if active cancer (overt evidence of cancer) or continuing to receive anti-cancer therapy

* Transient risk factors include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, prolonged travel (e.g. > 8 hours), lesser leg injuries or immobilizations more recently (e.g. within 6 weeks). The greater the provoking reversible risk factor (e.g. recent major surgery), the lower is the expected risk of recurrence after stopping anticoagulant therapy.

† Absence of a transient risk factor or active cancer.

‡ This decision is sensitive to patient preference.

¶ Indefinite therapy is suggested if there is moderate risk of bleeding, and 3 months is suggested if there is a high risk of bleeding; both of these decisions are sensitive to patient preference.

Although not a professional guideline body, the Canadian Agency for Drugs and Technologies in Health (CADTH) has published treatment recommendations for optimal treatment use. CADTH recommends that the standard of care for patients diagnosed with PE follow the approach of systematic anticoagulation with heparin (low-molecular-weight heparin [LMWH], administered subcutaneously) followed by oral administration of vitamin K antagonists (VKAs).[99] VKAs overlap with LMWH until sufficient anticoagulation with oral agents is achieved. To avoid

inadequate anticoagulation (associated with increased risk of recurrent VTE and PE), or supratherapeutic anticoagulation (associated with increased bleeding risk), the degree of systemic anticoagulation achieved with VKAs should be monitored with blood tests and dose adjustment.[99]

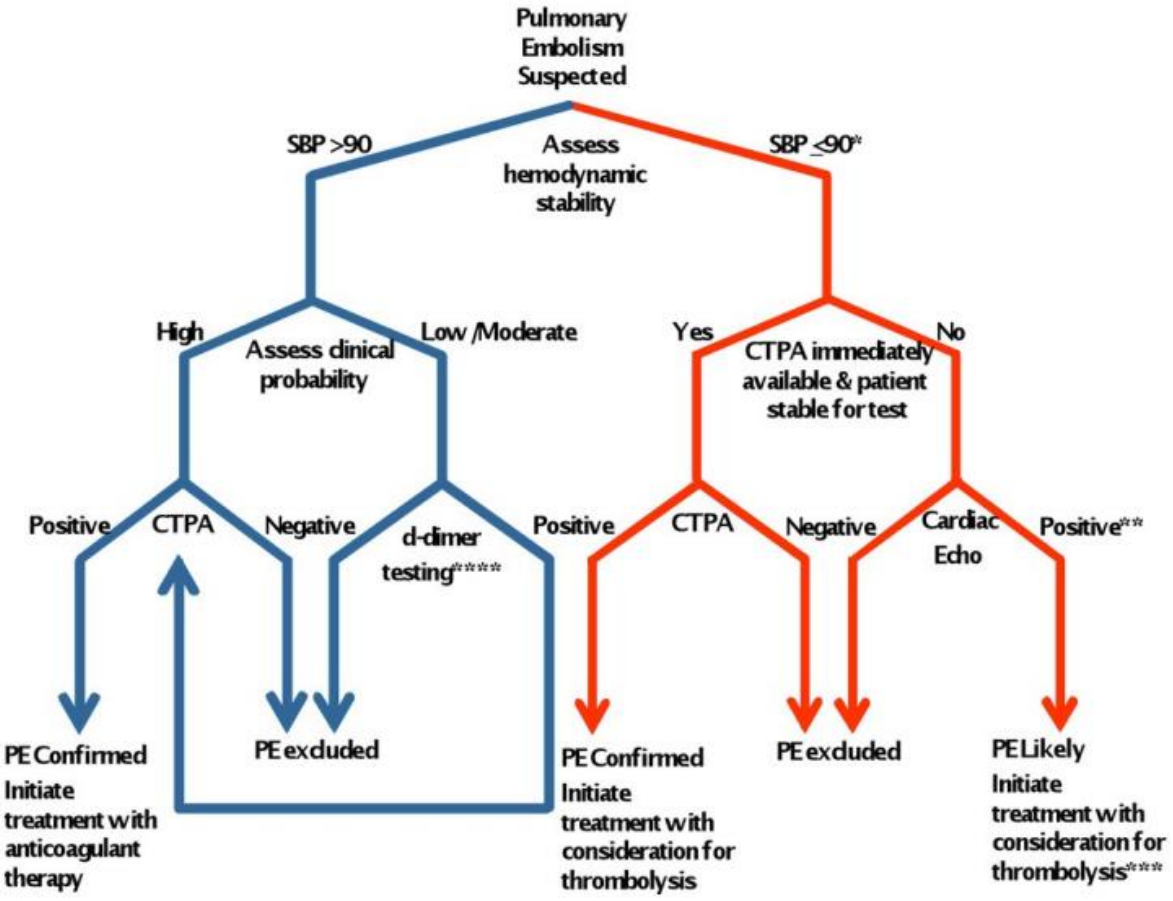
3.10 Clinical Practice Guidelines

3.10.1 Canadian Clinical Practice Guidelines

In 2015 Thrombosis Canada published a clinical guideline for all Canadian health care professionals with the intention of defining a diagnostic algorithm and treatment strategy for patients with acute PE.[100] Thrombosis Canada is a Canadian registered non-profit organization, which was established in 1991. This organization membership includes eminent and internationally recognized thrombosis experts, who have made many contributions to the body of knowledge in vascular medicine. The guideline recommends that clinical stability and pre-test probability dictate the diagnostic approach. The guideline provides a suggested diagnostic algorithm for suspected PE (Figure 6). In patients without hypotension, pretest probability should be assessed by an experienced clinician and possibly a validated clinical prediction rule such as the Wells Score. The guideline subsequently states the following recommendations for low to intermediate, and high pre-test probability of PE:[100]

- Low to intermediate pre-test probability: A negative D-dimer result rules out the diagnosis of PE. However, a positive D-dimer test should be followed by a definitive test to confirm or refute diagnosis.
- High pre-test probability: No value in checking a D-dimer level as a negative results' post-test probability would be unacceptably high. Thus, the patient should be taken directly to CT testing to establish diagnosis.
- Low clinical probability and in the absence of D-dimer testing: Diagnosis can be safely excluded using the PERC rule for PE.

Figure 6: Suggested Diagnostic Algorithm for Suggested PE[100]



SBP: Systolic Blood Pressure, CTPA: CT Pulmonary Angiography, PE: Pulmonary Embolism

For patients with an allergy to contrast dye in whom a CT would be contraindicated, the guideline suggests looking initially for evidence of DVT through lower extremity compressive ultrasound (CUS).[100] A positive result would mandate the same treatment as PE, and no further investigation is required. A negative result would also not rule out PE as up to 30% of patients will not have DVT and PE concurrently; in this case, a V/Q scan should be obtained. If CT is not readily available or if the patient has hypertension and is not able to undergo the scan, an immediate echocardiogram should be obtained to search for evidence of a right heart overload or a clot in the RV or pulmonary arteries. If this evidence is found and no alternative diagnosis is given, treatment for PE should be commenced.[100]

As referred to under the subheading "Treatment" above, Thrombosis Canada has also published a clinical guideline for the treatment of PE, with the aim of providing an evidence based approach to diagnosis and treatment of patients with acute PE.[97,101]

3.10.2 Calgary Clinical Practice Guidelines

Calgary, Alberta has established a program to aid in the diagnosis of PE, headed by the Calgary Zone Emergency Medicine Division. This program has designed a clinical decision support tool to align CT use for PE to appropriate practice[4]. This tool is integrated into the electronic management system (Sunrise Clinical Manager) in the Calgary zone.

When a physician orders a CT for a relevant patient encounter, the clinical decision support tool is triggered. The tool first queries whether the clinician suspects PE; if no, the physician is informed that the tool is not designed for this purpose, if yes, additional questions follow. The physician is asked whether the patient has any of the following exclusions: unstable patient, known DVT or PE, anticoagulation, or is pregnant. If none, the physician follows a series of questions to determine the patient's Wells score, including clinical signs and symptoms, heart rate, history of DVT or PE, and malignancy. Based on the calculated Wells Score, a recommended pathway is given. The pathway used for diagnosing PE within this clinical decision support tool is as follows:

- Wells Score <2: PERC, followed by D-Dimer and then CT
- Wells Score between 2 and 4: D-Dimer followed by CT
- Wells Score >4: CT, or if low-risk patient with normal chest x-ray, history of renal failure or history of serious intravenous (IV) contrast reaction, then VQ scan used

Based on 3-months post-intervention data, uptake of this clinical decision support tool has been 43%. Uptake of this tool varies depending on whether use is mandatory or voluntary; compliance varies between 0% and 75%, with the highest compliance being achieved at a site that mandated use, while sites with low compliance had voluntary use. Eight-month data

[4] The PE clinical decision support tool is available from the following link: https://cdst.cru.ucalgary.ca/pe/assessment_tool/2333/

suggests that the yield has increased from 14.50% to 15.10% in the intervention arm and decreased in the control arm from 14.3% to 14.0%. Moving forward, this program is considering options for incentives and disincentives to improve uptake.

3.10.3 St Joseph's Healthcare Program (Ontario) Clinical Practice Guidelines

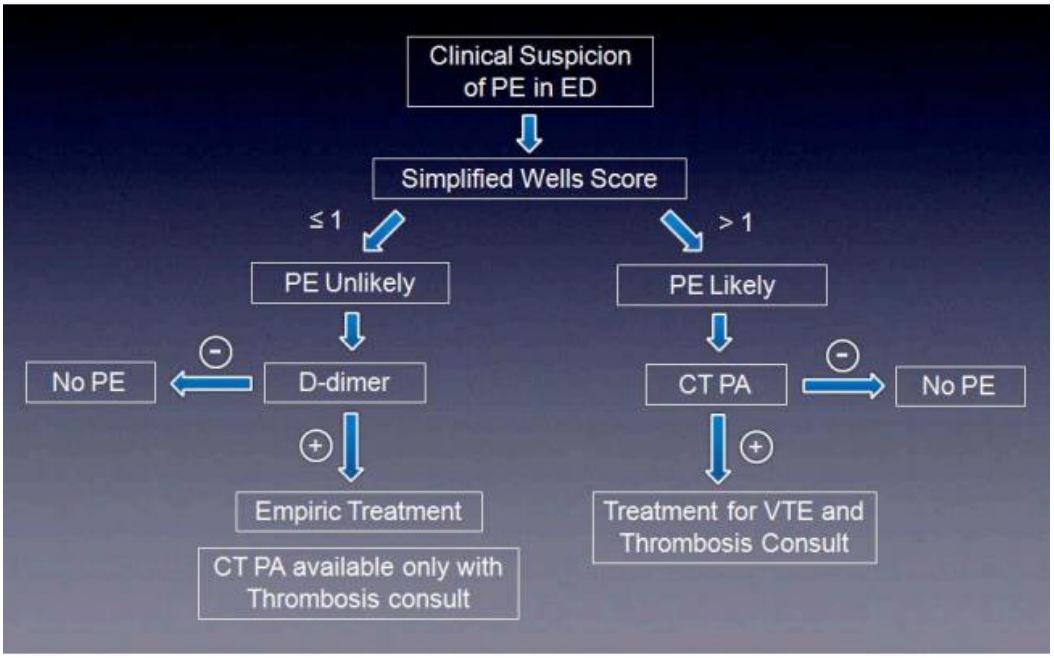
St. Joseph's Healthcare in Hamilton, Ontario implemented a clinical decision support tool incorporating the simplified Wells criteria in 2013, with the objective of decreasing the number of negative CT studies [102]. To evaluate the effectiveness of this program, 189 emergency room patients were studied retrospectively after implementing a standardized requisition requiring adherence to an algorithm based on the simplified Wells Score [102]. This clinical decision support tool was implemented January 1st, 2013, and data were collected from January-March 2012, and January-March 2013.

The pathway used for diagnosing PE within this clinical decision support tool is as follows [102]:

- Wells Score ≤1: D-dimer, followed by empiric treatment (CT only with thrombosis consult) as required
- Wells Score >1: CT, followed by treatment for VTE and thrombosis consult as required

This diagnostic pathway differs from that of Thrombosis Canada; it is unknown how this diagnostic pathway was developed and why it was chosen.

Figure 7: Diagnostic Pathway used at St, Joseph's Healthcare [102]



Using this tool, and diagnostic pathway, this program saw a 21.7% reduction in CT studies after introducing the algorithm, and an increase in the number of positive CT studies (yield) from 13.2% to 21.7%; however, this result was not statistically significant with a p-value of 0.12 [102].

3.11 Ongoing Research

The Canadian Agency for Drugs and Technologies in Health (CADTH) is currently completing a project on optimal strategies for the diagnosis of acute PE. This project includes an analysis of the optimal diagnostic pathway for diagnosing PE, including risk stratification strategies. The report will separately address the best strategies for urban, rural and remote settings. It is anticipated that this guidance on diagnostic pathways will be completed June, 2017.

4 Diagnostic Accuracy

- A total of 5341 citations were identified from the literature search. Of those, 373 proceeded to full-text review. An additional 357 articles were excluded following full-text review, and 14 articles were included in the final analysis
- The pooled sensitivity was 84.8% (95% CI 81.7% to 87.5%) and the pooled specificity was 93.0% (95% CI 90.9% to 94.6%).
- These results indicate CT is more effective at correctly identifying subjects without PE than correctly classifying patients with PE
- Only one study reported safety outcomes. This study found that <1% of participants experienced an adverse effect; all adverse symptoms were due to allergies to the contrast material used during CT.

4.1 Objective

To determine the diagnostic accuracy of CT for diagnosing PE

4.2 Methods

Medline, Pubmed, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect (DARE), Cochrane Central Register of Controlled Trials and CINAHL were searched from inception until September 13, 2016. Terms aimed at capturing the technology such as "CT," "CTPA," "Tomography Scanners," and "CT" were combined using the Boolean Operator "or." These terms were then combined, using the Boolean Operator "and" with terms describing the clinical condition, such as "pulmonary embolism," "venous thromboembolism," and "blood clot." Results were limited to English and French language studies, and conference abstracts were filtered out. No other limitations or filters were applied. Details of this search can be found in Appendix A.

All abstracts and titles were independently screened by two reviewers. Abstracts proceeded to full-text review if: included only adults 18 years or older who were undergoing testing for acute PE, assess CT technologies, report diagnostic test accuracy, clinical utility or harms, and were a randomized controlled trial, non-randomized study or case series. Abstracts were excluded if they failed to meet any of the above inclusion criteria, or if they: were single detector CT, did not report original data, were not available in French or English, were duplicate publications, or were case reports, conference abstracts, published thesis documents and evidence that has not been

peer-reviewed. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in Table 6. Full-text review was completed in duplicate. Any discrepancy between reviewers was resolved through discussion, or consultation with a third reviewer when necessary. Reference lists of identified eligible studies were hand searched to ensure all relevant articles were captured in the search. In addition, articles identified by content experts were assessed for eligibility.

Table 6**.** Inclusion and Exclusion Criteria for Clinical Systematic Review

Inclusion Criteria	Exclusion Criteria

• Adult patients 18 years or older
• Undergoing testing for acute PE
• Assessed CT technologies
• Reports at least one of the following outcomes:
  o Diagnostic test accuracy
  o Clinical utility (efficiency, change in diagnostic thinking, change in patient management, change in patient outcomes, identification of patients with different diagnoses)
  o Harms (radiation exposure, CT attributed malignancy, contrast nephropathy, allergic reactions)
• Study designs including:
  o Randomized controlled trials, non-randomized study, case series
	• Single detector CT
	• Not original data
	• Full-text not available in French or English language
	• Case reports, conference abstracts, published thesis documents and evidence that has not been peer-reviewed
	• Duplicate publications

For all studies, data were extracted using standardized data extraction forms which were designed a priori to document all relevant information from included studies. Data extraction was conducted in duplicate by three teams of reviewers. All six reviewers piloted the data extraction

forms using randomly selected included studies until consistency amongst reviewers was reached. Once consistency was reached, data from each included study was extracted by one reviewer and checked for accuracy by a second reviewer. Data on study characteristics, methodology, included patients and outcomes were extracted. Discrepancies between reviewers during data extraction were resolved through discussion, or involvement of a third reviewer when necessary. Authors from included studies were contacted to clarify any issues or provide any missing information.

Three quality assessment tools were used, due to the heterogeneity of study design included in this systematic review. Randomized Controlled Trials (RCTs) were assessed using the Cochrane Risk of Bias checklist [103]. Using this checklist, each study was assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and any additional potential sources of bias) [103]. Each study is assigned "low, "high," or "unclear" risk of bias for each of these seven potential sources of bias.

The quality of diagnostic accuracy studies was assessed using the QUADAS-2 tool[104]. The previously published QUADAS-2 tool consisted of 11 signaling questions or assessment items across four key domains: (1) patient selection; (2) index test; (3) reference standard; and (4) patient flow and timing [104].

The quality of non-comparative studies assessing safety of CT were assessed using the Moga Checklist. This checklist assesses quality of studies in seven areas: study objective, intervention and co-intervention, outcome measures, statistical analysis, results and conclusions, competing interests and source of support. Within these seven domains, eighteen questions are assigned "low," "high," or "unclear" risk of bias.

A narrative synthesis of all included studies is presented below. In addition, a meta-analysis was conducted. Sensitivity and specificity of CT were the primary outcomes. Sensitivity quantifies the ability of a test to correctly identify those with the target clinical condition (PE), whereas specificity quantifies the ability of the test to correctly identify those without PE. The sensitivity

(true positive rate) and specificity (true negative rate) values of CT in diagnosing PE were extracted from each included study and subsequently combined. *Cochrane Q* and χ^2 statistics were used to examine the heterogeneity of the included studies. A bivariate random effect model was used in order to take the two-dimensional nature of the diagnostic accuracy data into account[105]. The model results in pooled point estimates of sensitivity and specificity together with a confidence region. Further, a summary receiver operating characteristic (ROC) curve, which provides information on the overall performance of CT in diagnosing PE through different thresholds, was also obtained. In addition, from each included study, information on the type of CT device used, relevant scan parameters and reference standards were extracted. All analyses were completed in R using R package *mada* [106].

4.3 Results

A total of 5341 citations were identified from the literature search. Of those, 4968 were excluded during abstract review and 373 proceeded to full-text review. An additional 357 articles were excluded following full-text review, and 14 articles were included in the final analysis (Figure 8).

4.3.1 Characteristics of Included Studies

Fourteen studies assessing diagnostic accuracy of CT were included; one randomized controlled trial, ten prospective non-randomized studies and three retrospective non-randomized studies. Characteristics of each included study have been synthesized in Table 7, and in Appendix A. Three studies were conducted in China [107-109], two in United States [110,111], two in France [112,113], two in Germany [114,115], and one in each: Japan [116], Switzerland [117], Belgium [118], and Sweden [119]. The studies were published between 2000 [112,113] and 2015 [116].

The number of participants included in each study varied between 48 [111] and 773 [120], with a total of 2633 participants included in all fourteen studies combined. The inclusion and exclusion criteria varied across studies. However, for all patients, there was a clinical suspicion of PE at the point of inclusion.

Figure 8: Flow Chart

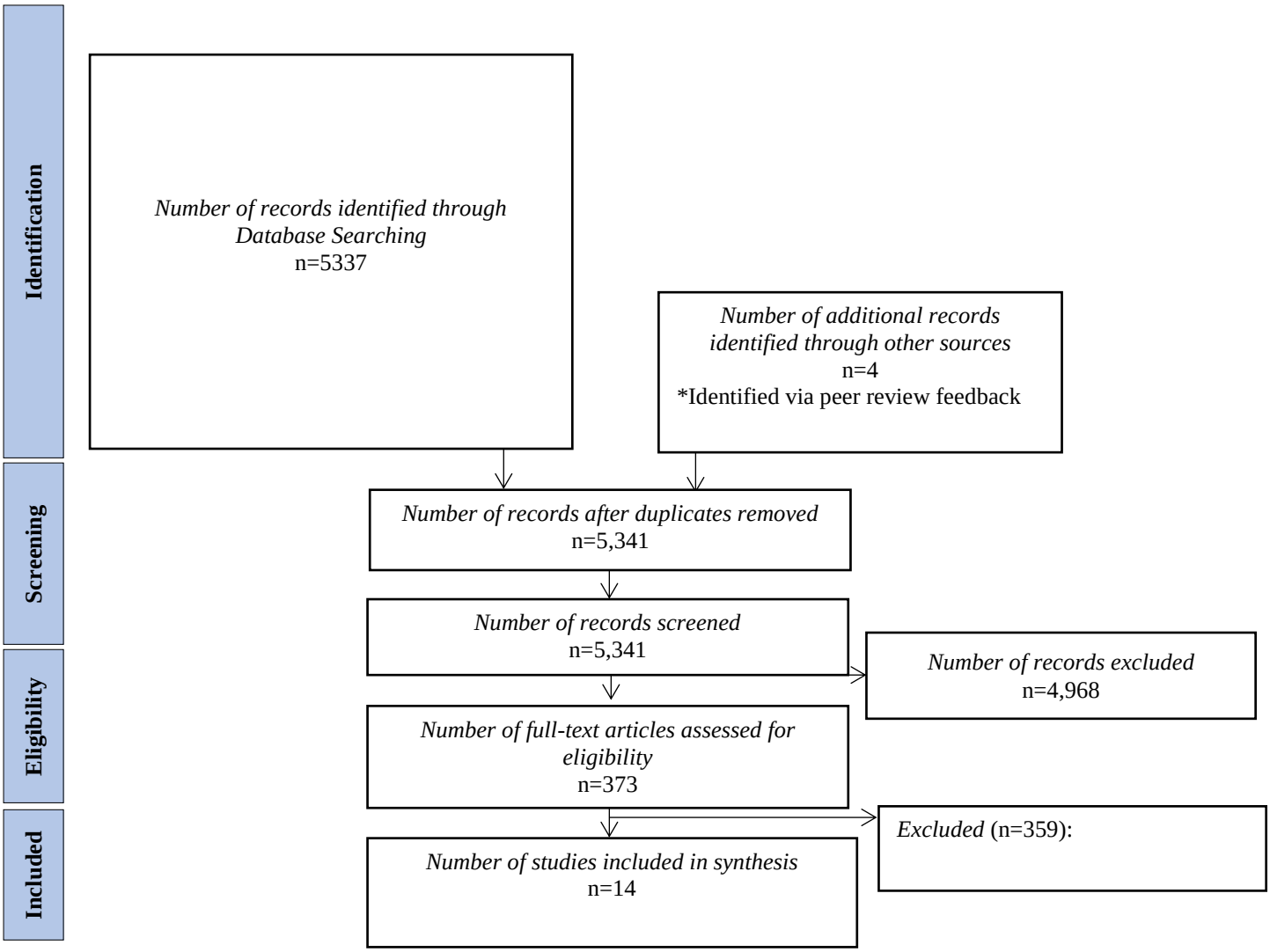


Table 7: Synthesis of Characteristics of Included Studies

Author, Year, Country	Study Details	Intervention	Outcomes Measured
Lu, 2014 China	*Study Design:* RCT *Setting of conduct:* single center. Imaging unit of a hospital. *Number of included participants:* 100	*Intervention*: Dual source CT *Reference Standard*: Consensus reading	Image quality, diagnostic accuracy and radiation dose
Megyeri, 2014 Switzerland	*Study Design:* Retrospective NRS *Setting of conduct:* single center. Emergency care unit of a tertiary-care center *Number of included participants: 123 (Body Weight > 100kg); 114 (Body Weight < 100 kg)*	Intervention: Multi detector CT Reference Standard: Composite reference standard	Diagnostic accuracy of CT in two patient groups
Okada, 2015 Japan	*Study Design:* Retrospective NRS *Setting of conduct:* single center. Setting unclear. *Number of included participants:* 83	Intervention: Multi detector CT Reference Standard: CT / LPBV + clinical and physical findings	Number and locations of intra-pulmonary clots, Diagnostic accuracy values
Stein, 2006 International	*Study Design:* Prospective NRS *Setting of conduct:* Multi center. Inpatient or outpatient clinical centers *Number of included participants:* 773	Intervention: Multi detector CT Reference Standard: Composite reference standard	Diagnostic accuracy of CT
Coche, 2003 Belgium	*Study Design:* Prospective NRS *Setting of conduct:* single center. Emergency department of urban teaching hospital with an annual census of 50,000 patients *Number of included participants:* 94	Intervention: Multi detector spiral CT Reference standard: Ventilation-perfusion (V-P) scintigraphy, pulmonary digital subtraction angiography when indicated, and chest radiography	Episodes of recurrent or new deep venous thrombosis or PE; Diagnostic accuracy of CT
Quandli, 2000 France	*Study Design:* Prospective NRS *Setting of conduct:* single center. Department of radiology *Number of included participants:* 158	Intervention: Dual section helical CT Reference Standard: Pulmonary Arteriography	Presence of PE, Diagnostic accuracy of CT
Wang, 2009 China	*Study Design:* Prospective NRS *Setting of conduct:* single center. Department of internal medicine *Number of included participants:* 82	Intervention: Multi detector CT Reference Standard: based upon all imaging modalities, all available laboratory recorders, clinical data, the opinions of the physicians responsible for treatment and outcomes. .	Diagnostic accuracy of CT
Winer-Muram, 2004 USA	*Study Design:* Prospective NRS *Setting of conduct:* single center. emergency room and inpatient populations of tertiary care center and a public hospital	Intervention: Multi detector CT Reference Standard: Pulmonary Arteriography	Presence of PE, Diagnostic accuracy of CT

	Number of included participants: 93		
Blachere, 2000 France	*Study Design:* Prospective NRS *Setting of conduct:* single center. inpatients, outpatient, intensive care unit *Number of included participants:* 179	Intervention: Helical CT Reference Standard: All patients underwent ventilation–perfusion radionuclide lung scanning, contrast-enhanced helical CT angiography, and Doppler sonography of the legs	Recurrence of PE or of a VTE Diagnostic accuracy of CT
Ohno, 2004 USA	*Study Design:* Prospective NRS *Setting of conduct:* single center. Setting unclear *Number of included participants:* 48	Intervention: Multi detector CT Reference standard: pulmonary angiography	Diagnostic accuracy of CT
Reinartz, 2004 Germany	*Study Design:* Retrospective NRS *Setting of conduct:* single center. Setting not reported. *Number of included participants:* 83	Intervention: Multi slice spiral CT Reference Standard: Consensus reading	Diagnostic accuracy of CT
Reissig, 2001 Germany	*Study Design:* NRS *Setting of conduct:* single center. Setting not reported. *Number of included participants:* 69	Intervention: Spiral CT Reference Standard: CT and transthoracic sonography	Diagnostic accuracy of CT
He, 2012 China	*Study Design:* NRS. Cross sectional *Setting of conduct:* Multi center. Secondary care centers (including academic centers). *Number of included participants:* 544	Intervention: Multi detector CT Reference Standard: clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g., echocardiography), CT, V/Q, right heart cardiac catheterization, and PA (performed in patients with indeterminate tests by other modalities) as well as physician opinions and 6-month clinical follow-up	Diagnostic accuracy of CT
Nilsson, 2002 Sweden	*Study Design:* Prospective NRS *Setting of conduct:* Single center. Emergency ward. *Number of included participants:* 90	Intervention: Spiral CT Reference Standard: Pulmonary Angiography	Diagnostic accuracy of CT

NRS: Non-randomized Study

Each study has used its own CT scan protocol with different scan parameters. Table 8 summarizes the variation of common scan parameters across studies. Four studies have used a composite reference standard that was a combination of clinical probability, additional imaging, follow-up, all available laboratory records and physicians' opinions, as the reference method to derive diagnostic ability of CT [108,109,117,120]. Four studies have used combined imaging tests that include two or more of CT, transthoracic ultrasound, ventilation-perfusion, Doppler sonography, and Pulmonary angiography, as the reference method [113,115,116,118]. Pulmonary arteriography / angiography was used as the reference method in another four studies [110-112,119]. Two studies have used consensus reading as the reference standard [107,114].

Table 8: Between study variability of CT scan parameters

Study	Scan parameters					
	Device	**Tube potential**	**Tube current**	**Scan time**	**Collimation**	**Pitch**
Lu, 2014	Dual source CT	80 kVp	110 mA	-	64 x 0.6 mm	Routine pitch
Megyeri, 2014	Multi detector CT	100 kVp	100 mA	-	16 x 0.75 mm	2.2
Okada, 2015	Multi slice dual source CT	120 kVp	-	-	64 x 0.6 mm	0.5
Stein, 2006	Multi detector CT	120 kVp	400 mA	0.8 s	1.25 mm	1.5
Coche, 2003	Multi detector spiral CT	120 kVp	144 mA	0.5 s	4 x 1 mm	1.25
Qanadli, 2000	Dual section helical CT	120 kVp	199 mA	20 s	2 x 2.5 mm	1.5
Wang, 2009	Multi detector CT	-	-	-	-	-
Winer-Muram, 2004	Multi detector CT	120 kVp	200 - 300 mA	14 - 17 s	4 x 2.5 mm	1
Blachere, 2000	Helical CT	120 kVp	170 mA	0.75 s	variable	1.8 - 2.0
Ohno, 2004	Multi detector CT	140 kVp	110 mA	-	4 x 1 mm	6:1
Reinartz, 2004	Multi slice spiral CT	120 kVp	100 mA	20 s	4 x 1 mm	-
Reissig, 2001	Spiral CT	-	-	-	-	-
He, 2012	Multi detector CT	120 kVp	300 mA	-	64 x 0.625 mm	-
Nilsson, 2002	Spiral CT	120 kVp	200 - 210 mA	-	3 mm	-

4.3.2 Reported Outcomes

Diagnostic accuracy (sensitivity and specificity) of CT was the primary outcome reported in all included studies. In addition, one study [120] reported safety outcomes such as mild allergic reactions (itching, swollen eyelid or vomiting) (<1% of patients), urticarial (<1%), and moderately severe extravasation of contrast material into the antecubital fossa (<1%). Further, five studies [108,112,113,118,120] have reported percentage of indeterminate CT examinations that range from 1% [118] to 6% [120].

4.3.3 Quality of Included Studies

Randomized Controlled Trials

Cochrane Risk of Bias for Randomized Controlled Trials was used to quality assess the one included RCT[107]. The RCT assessed showed a high or unclear risk of bias mainly due to unclear methods of random sequence generation and due to difficulty to assess allocation concealment (Table 9).

Table 9. Quality Assessment of Included Randomized Controlled Trial

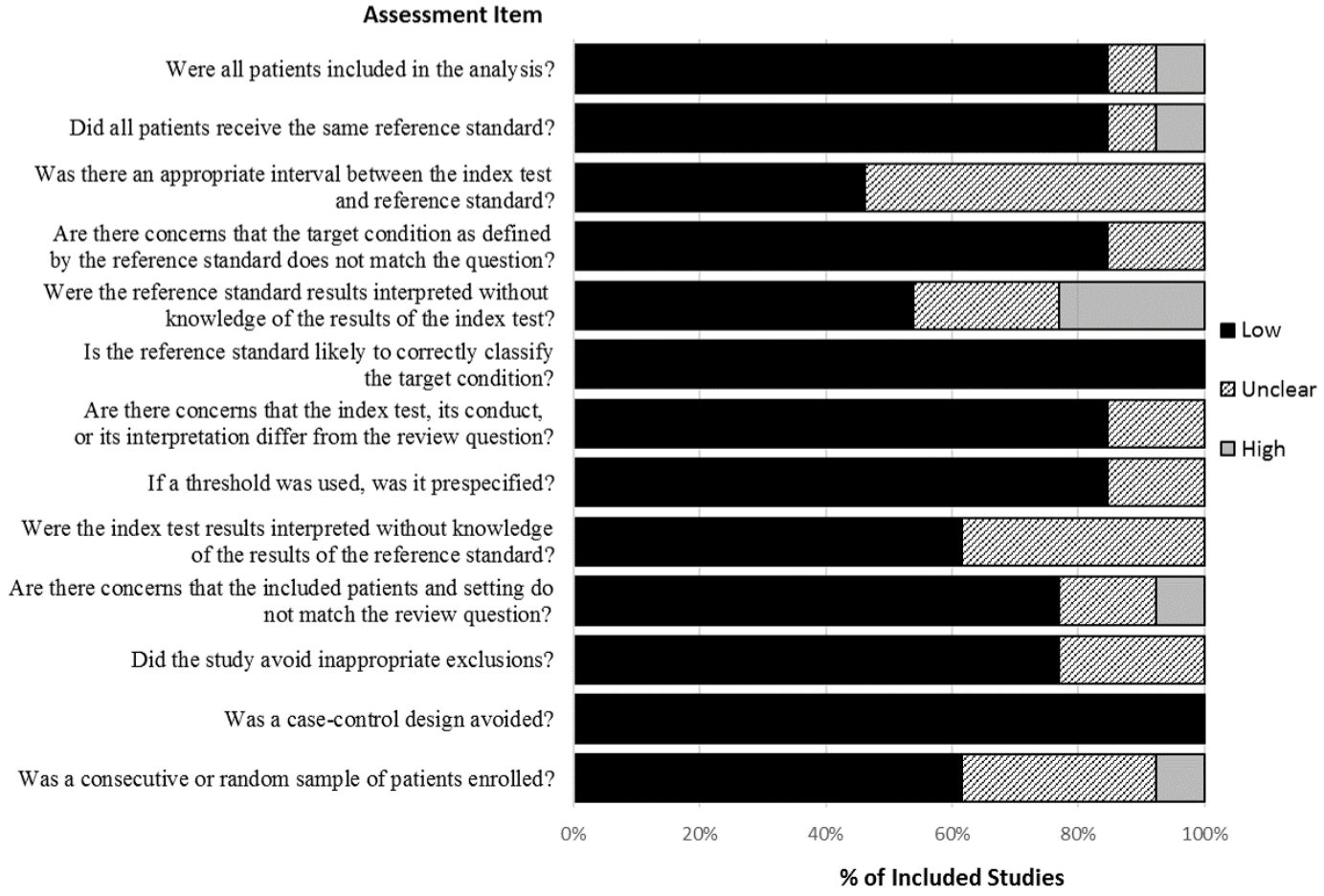
Author	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Participants and Personnel**	**Blinding of Outcome Assessment**	**Incomplete Outcome Data**	**Selective Reporting**	**Any Other Bias?**
Lu[107], 2013	High	High	Unclear	Low	Low	Low	Unclear

Non-Randomized Diagnostic Accuracy Studies

The methodological quality of the included diagnostic accuracy studies was assessed using the 10-item QUADAS-2 tool [104]. Ratings for the 10 signaling questions or assessment items for each study are summarized in Figure 9, and the full quality assessment can be found in Appendix A. Given that weights are not assigned to each of the assessment items, no overall or tallied quality score was used. One non-randomized study has assessed as having a low risk of bias in all four areas of QUADAS-II scheme [119]. None of the remaining studies received 'Yes' responses to all 10 signaling questions contained in the QUADAS-2 assessment tool, suggesting that each was subject to at least one source of potential bias. One study was assessed as having high risk of bias in one of the four areas [115].

Broadly, lack of information on patient inclusion/exclusion criteria, un-blinded assessors and participants, and unclear information about the timing of index and reference tests were the main reasons for a study to be assessed as having an unclear or high risk of bias.

Figure 9: Assessment of quality item for all included non-randomized studies. Proportions of studies rated as "Low", "Unclear" and "High" for each QUADAS-2 item.



4.3.4 Meta-analysis of Diagnostic Accuracy of CT

All 14 studies were included in the meta-analysis despite differences in scan parameters. Discussion with a clinical expert found these differences to have minor effect on diagnostic accuracy of multi-detector CT, and therefore, all were included. In the meta-analysis, an assumption was made that all reference standard tests had the same ability to correctly classify PE. Many reference standard tests were used, such as consensus reading of CT results, composite reference standards, and pulmonary angiography. It is possible that some of these reference

standards are more accurate at determining the true state of PE than others. This is a limitation of this analysis.

Figure 10: Sensitivity and specificity reported in included studies

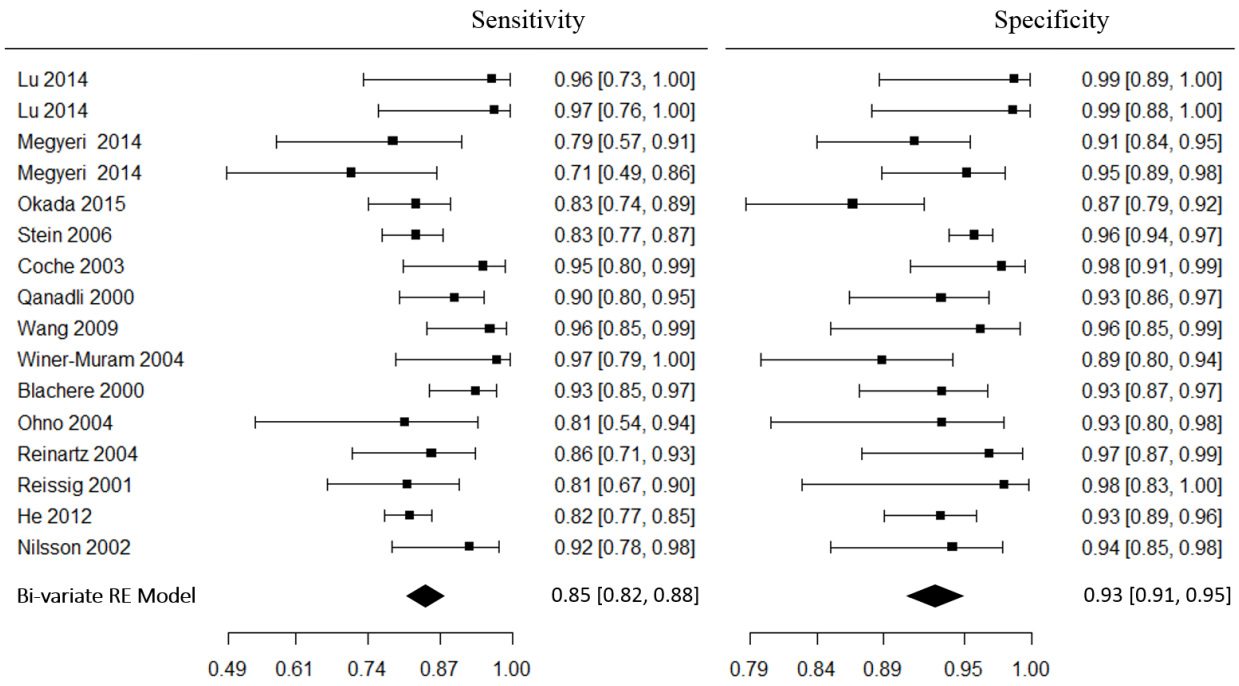
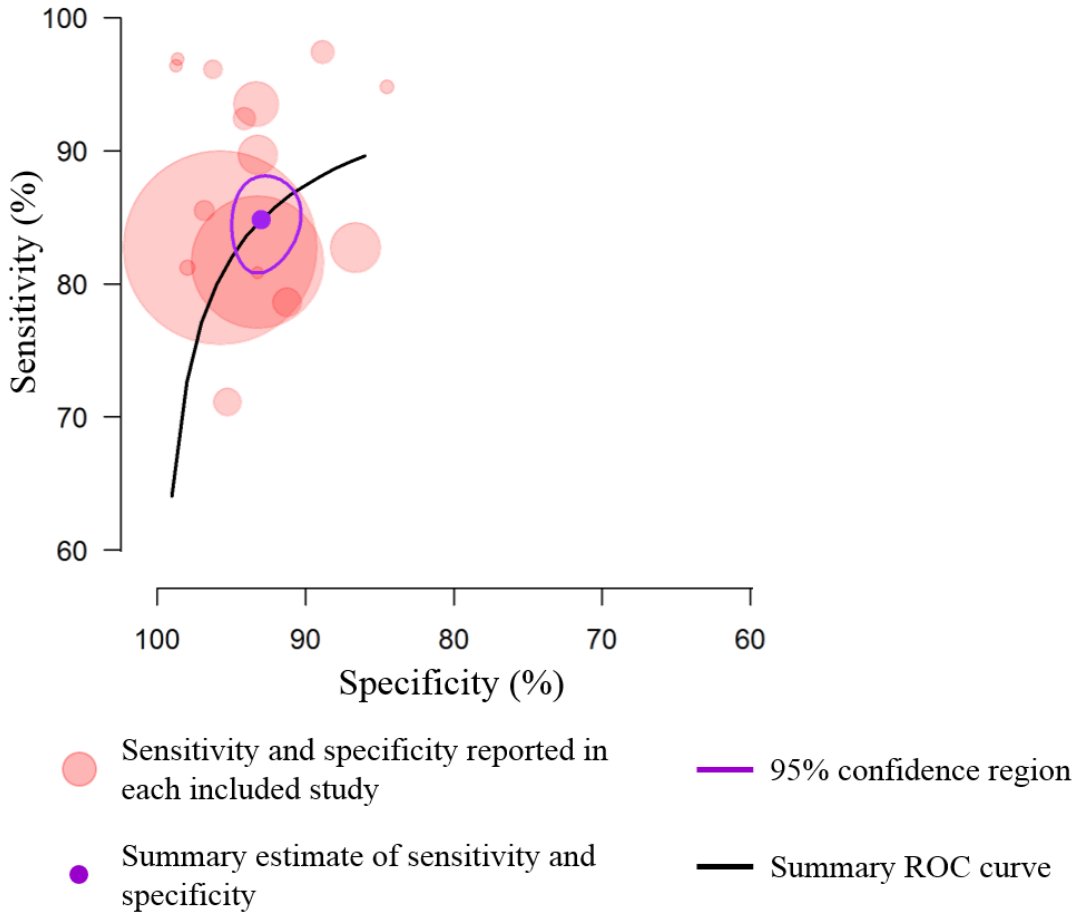


Figure 2 shows sensitivity and specificity reported in each study. Univariate meta-analyses indicated that the studies were marginally heterogeneous in terms of sensitivity (P = 0.04) and specificity (P = 0.05). In order to address this possible heterogeneity and to take the obvious correlation between these two entities into account, a bi-variate random effect model was carried out. Figure 3 shows the resulted summary ROC curve, the point estimates of pooled sensitivity and specificity and their confidence region. The pooled sensitivity was 84.8% (95% CI 81.7% to 87.5%) and the pooled specificity was 93.0% (95% CI 90.9% to 94.6%). Results indicate that CT has higher ability to identify subjects without PE correctly compared to its ability to correctly classify patients with PE.

Two studies have used consensus reading as the reference standard to obtain diagnostic accuracy of CT. This method is not as accurate as the other reference standards in correctly classifying PE patients as it highly depends on the readers' (or radiologist's) viewpoint. In order to assess the

effect of these two studies on the results, we repeated the Meta-analysis excluding those studies. The change in pooled diagnostic accuracy values was not significant (sensitivity 83.6% and specificity 93.2%).

Figure 11: Receiver operating characteristics (ROC) plot displaying diagnostic accuracy of CT reported in each included study and summary estimates obtained from the bi-variate random effect model. Size of each data point is proportional to the sample size of the corresponding study.



4.4 Conclusions

Fourteen studies were included in this systematic review and meta-analysis. All included studies were considered in the meta-analysis despite the differences in scan parameters and reference standards. The pooled sensitivity of CT for diagnosing PE is 84.8% and the pooled specificity is

93.0%. These results indicate that CT is a highly specific but moderately sensitive diagnostic modality for PE. That is, CT is more effective at correctly identifying subjects without PE than correctly classify patients with PE. Overall, CT is a good diagnostic tool, and there is opportunity to combine it with other tests to improve the diagnostic accuracy. Given the low risk of treating for PE, false positives produce a minimal risk.

5 British Columbia Context and Physician Perspectives

Summary

- Five key informant interviews were conducted by a qualitative researcher to gain insight into the current ED physician experience in British Columbia with diagnosing PE
- Several challenges, barriers and facilitators for improving the PE diagnostic pathway were identified, including how to decrease inappropriate use of CT

5.1 **Purpose**

To gain insight into the current emergency room clinician experience in British Columbia, the diagnostic pathway for PE, and where CT scans fit in this pathway.

5.2 Methods

Key informant interviews were conducted with emergency department (ED) physician leaders. A semi-structured interview guide was developed to guide the interviews; questions were aimed at determining current approaches to diagnose PE across Canada. This guide evolved over the course of the interviews, as questions were refined to reflect what was learned through previous interview(s). All the interviews were audiotaped with the consent of the interview participants and detailed notes were taken. The notes and voice files were reviewed with the purpose of identifying key themes and important points related to the policy questions being posed.

5.3 Findings

Interviews were conducted with five ED physicians between February and March 2017; two physicians were from Interior Health; one from Vancouver Coastal; one from Vancouver Island; and one from the Fraser Valley. We were unable to conduct an interview with a physician from the Northern health region. Two of the physicians interviewed had experience as provincial emergency transport advisors, providing support to paramedics and other health professionals in rural and remote communities.

5.3.1 Clinical Experience

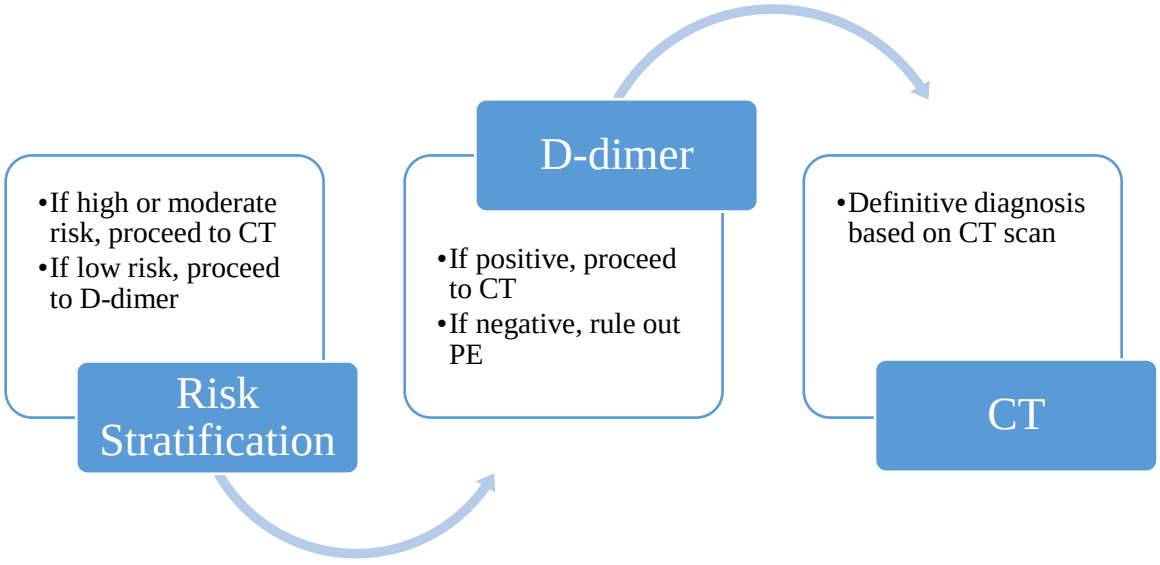
Undifferentiated chest pain, shortness of breath, and undifferentiated abdominal pain are the most common complaints of patients presenting to the ED. Due to this, it is a common

experience for ED physicians to proceed along a diagnostic pathway with the intent to rule out or diagnose PE. One interviewee said, for example, that of the 240 visits a day to their busy large urban hospital ED, approximately 10% of those present with shortness of breath and chest pain. These were described as "not quick patients", all ranked a 2 or 3 on the Canadian Triage and Acuity Scale (CTAS), meaning that they spend 3-4 hours in the ED.

5.3.2 Diagnostic Pathway

Physicians were asked to describe the process they follow to diagnose or rule out PE. All described the following pathway:

Figure 12: PE Diagnostic Pathway



- If there is some reason why a CT scan is considered to be risky, then a dose of anti-coagulant may be given to see if this improves the patient's symptoms
- Other kinds of imaging (MRI, V/Q SPECT) are rarely done, primarily due to extra resources required (e.g. time, expertise, specialized equipment)

5.3.3 Risk Stratification Criteria

All interview participants identified a risk stratification tool was used at the beginning of the diagnostic pathway. Four of the five interviewees mentioned using the PE Rule-Out Criteria (PERC), two the Wells Criteria, and one the revised Geneva score; with some using more than one. Some physicians described these criteria as being of limited use in determining whether a patient might have a clinically important PE. A contributing factor to this may be the lack of comprehensive clinical practice guideline and, not knowing where risk stratification should fit in the diagnostic pathway.

5.3.4 D-dimer *testing*

There was frequent discussion about problems with D-dimer testing. For example, recently there has been increased discussion about the role of age-adjusted D-dimer. As one physician noted: what would help is a rule of next steps for positive D-dimer (most of people with a positive D-dimer, have a negative CT or ultrasound), what next? That is, in order to cut down on the ordering of CT scans, restricting the use of D-Dimer testing might be a good idea. For example, you would not order a D-Dimer if someone was post-operative or had experienced trauma, as it will always be positive.

5.3.5 *Imaging*

The CT scan was described by physicians as the "gold standard" for diagnosing PE. In the ED context, the goal is to get an accurate diagnosis so the patient can be admitted or discharged quickly. Many hospitals have CT scanners and the capacity to do a contrast CT; physicians see CT scans as easy to order. *"Even smaller sites with few radiologists can do and read CT."* Fifty-seven hospitals in BC use CT to diagnose PE, ranging from less than 5 to 76 patients diagnosed using CT per year per hospital.

Since CT provides a definitive answer at point of care that is also able to provide alternative diagnoses (e.g., lung cancer, pneumonia, coronary artery calcification), physicians consider CT an ideal test for the ED. Yet, the *"yield of PE from CT is really, really low."* There was recognition that many unnecessary CT scans are being done for "*something that we know is low probability and low yield."*

Some physicians described ordering a chest x-ray prior to CT in low risk patients with a positive D-Dimer blood test. X-ray is preferred to ultrasound since ultrasound takes more time to order and complete, and ultrasound staff are not on-call 24 hours/day. As one physician noted, it takes "*hours and hours*" to get an ultrasound versus a CT. *"If you are a patient and you don't feel very good, would you wait around 4 hours to get an ultrasound?"*

In British Columbia, ventilation/perfusion imaging (V/Q) is rarely used, as it is logistically challenging and time consuming. Many communities lack access to it. For example, one physician said he has ordered a V/Q 1 or 2 times in his ten years of practice. This test is booked on an outpatient basis. The main indications for a V/Q are "*vanishingly rare",* and its use would only be considered when CT radiation poses an extreme risk to a patient and/or when a patient is extremely obese.

5.3.6 ED Physician's Perspective on the Patient Experience

At a societal level, there is low awareness of PE, and types of imaging required for diagnosis. The patient experience with this diagnostic process was described by ED physicians as being variable, as patients with a possible PE present to the ED with various symptoms. They come from all age groups and backgrounds; some present with minor symptoms, while others are critically ill. The initial workup can be anxiety-inducing, upsetting, and/or stressful for patients.

For patients who are not seriously ill, it is important to recognize other factors that will impact their ability to stay in the ED to get a diagnosis confirmed. For example, patients will have competing time demands such as work, children and pets and other factors such as the expense of parking will impact whether a patient stays or leaves the ER. One physician working in a busy urban ED that serves a diverse group of people described the importance of understanding patients' expectations, and ensuring good communication throughout the patient's ED experience.

The development of a decision support tool (discussed below), was described as being useful for supporting conversations with patients and engaging them in shared decision making. Ideally, a

decision to not order a particular test would be made together by the patient and physician. For example, the patient needs to feel comfortable about a decision to not order a CT, and therefore needs to understand the weighting of risks and benefits.

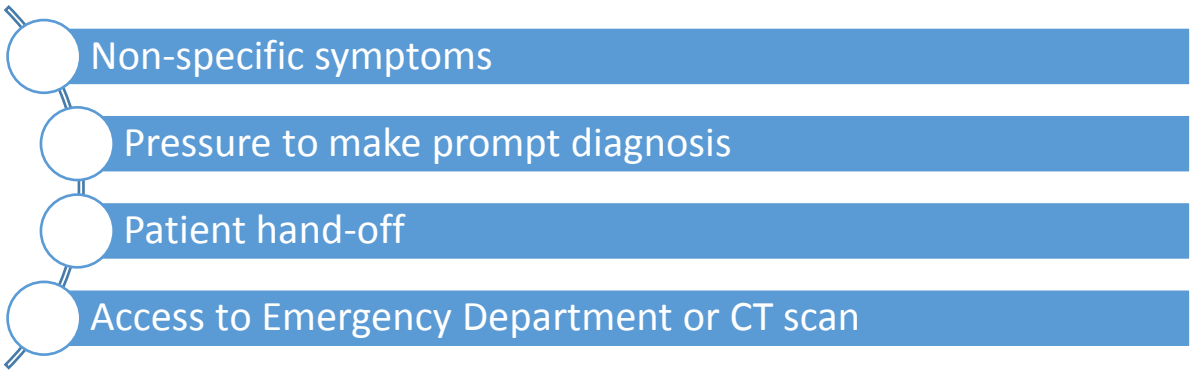
5.3.7 Challenges of Diagnosis

All physicians described challenges in ruling out or diagnosing PE because of the diverse and non-specific range of possible symptoms (Figure 13). As one interviewee noted*: "As the years go on, I realize PE is difficult to diagnose. It is a mimicker of many things."* If patients are very ill and there is suspicion of PE, a physician often does a CT quickly. However, if there is more time to deliberate, a more complex diagnostic pathway may be used, including trying to determine whether a possible PE might be clinically significant.

There are societal, healthcare system, and ED contextual issues that make prompt diagnosis of PE a priority and a challenge. ED physicians feel substantial pressure not to miss a PE, and want to be able to diagnose or rule out a PE before the patient leaves the ED. This is more challenging if the patient is not presenting as seriously ill.

A contributing factor to this is the challenge often experienced in handing off follow-up care to another physician. Some patients do not have family physicians and/or are unable to get an appointment to see their family physicians quickly. As a result, patients cannot access timely primary care, and in some cases also have no home or phone; in these cases, the burden of testing falls on the ED. Further, a lack of integrated and coordinated care in transitioning patients out of the ED poses additional challenges to physicians. As one physician described, ED physicians want to *"unburden themselves at the end of the shift",* and make the diagnosis quickly so that the patient can be discharged rather than handed over to another physician. These human factors are important.

Figure 13: Challenges of Diagnosis



In the ED context, with the pressure to make an accurate diagnosis as quickly as possible and with the easy access to CT scans to support this, CT scans tend to get ordered. Another recent contextual factor that is influencing an increase in the ordering of CT scans is that the shift in the risk of renal damage from the use of the CT contrast material has been determined to be less than previously thought. As this risk decreases, then the ordering of CT scans will increase; the balance of potential risk and benefit has shifted.

In rural and remote areas, where there is no access to an ED or a CT scan, the complexity gets magnified. Again, patients assessed as being at moderate or high risk of a PE are routinely transported, but when assessed as low risk the decision-making becomes more challenging. Transporting a patient to a larger centre is both disruptive to the patient and their family and uses considerable system resources.

5.3.8 Improving the PE Diagnostic Pathway

The physicians interviewed provided a number of suggestions for how the PE diagnostic pathway might be improved, and how inappropriate use of CT scans can be reduced. These included:

- Clearly defining what a serious PE is
- Development of an evidence informed decision support tool
- Physician education on complex presentation of PE, and the use of decision support tools
- Provision of a hospital-based thrombosis or transition clinic that would accept patients when the diagnosis is still outstanding

All physicians described the nuanced presentation of PE, and some described the ability of new CT scanner types to diagnose small PE's that would never have caused the patient any harm. Physicians said it would be helpful to know what size of PE is safe, and what amount of risk is safe. As one physician noted *"no one has come together to design what a 10% risk of blood clot looks like and how to proceed."*

All described the importance of developing evidence-informed decision support tools for diagnosing PE, but recognized that this would be a difficult task given some of the challenges described previously (e.g., often no clear mechanism of injury; a highly heterogeneous population). Benefits were described as the opportunity to build in decision analysis and a clinical scoring system, supporting decisions regarding what tests to conduct. A decision support tool that is well accepted by the medical community was described as supporting the ED physician's clinical decision to rule out PE. As one physician noted, you need something that shows that you went through an evidence informed list of findings to support no imaging of low-risk patients. The reality is that missing a clinically important PE is much riskier for the patient than missing an ankle fracture. This makes the need for clear rules, if they are possible to develop for PE, very important.

Other than risk stratification tools, none of the physicians interviewed were aware of any decision support tools or clinical practice guidelines, to support diagnosis of PE. As described previously, an important component of a decision support tool would be clear criteria regarding when to order a D-Dimer. All interviewees felt that a good decision support tool would be valuable, even more so in rural and remote areas regarding the need to transport for a CT scan. With respect to who might develop such a tool, suggestions included a collaborative effort involving the Canadian Association of Emergency Physicians, the Heart and Stroke Foundation, hematology, internal medicine, pulmonology, and radiology. One physician thought that the Emergency Strategic Clinical Network in Alberta might be well positioned to develop a tool.

Physicians who had experience with the implementation the clinical practice guidelines and decision support tools described how important it is to develop these tools and implementation

strategies collaboratively with physicians who will use the tool. One physician described a recent failed experience in one health region, where the radiology department tried to get ED physicians to provide a risk stratification score for PE before they could order a CT scan.

Physicians who had experience with referring patients who needed more follow-up to a thrombosis clinic, found that resource helpful. Access to such a clinic can help to decrease pressure on the ED physicians to make an immediate diagnosis, particularly in cases where the patient is not critically ill and has been assessed as low risk.

5.3.9 Embedding Decision Support Tools in Electronic Medical Records

Health regions in British Columbia are at various stages of implementing electronic medical records (EMRs) meaning that it is not yet possible to embed pop-up decision support tools (DSTs) in EMRs across the province. Physicians who have experience with pop-up tools in other settings felt that they could be helpful and are better than paper-forms. As described previously, however, developing these tools in collaboration with ED physicians is important.

In addition, for something as complex as PE, a physician education campaign would be important. Optimally, such a campaign would include online education and would also provide opportunities for physicians to discuss the nuances around diagnosing PE such as determining when a PE is clinically important (e.g., through physician rounds and journal clubs).

5.4 Conclusion

Diagnosing or ruling out PE is a complex endeavour. The patient population is heterogeneous, the symptoms general in nature, and it can be challenging to determine whether a PE is clinically significant. There are societal, healthcare system and ED contextual factors that influence the PE diagnostic pathway and contribute to over-ordering of CT scan. Not diagnosing a clinically important PE may have severe negative consequences; there is significant fear in the medical community about missing this diagnosis. Lack of access to follow-up primary care or other kinds of transitional care puts pressure on ED physicians to make a diagnosis or rule out PE before the patient leaves the ED. The physician interviews were unaware of any good decision support tools for diagnosing PE that would help decrease the inappropriate use of CT. Physicians, recognizing

that such a tool would be challenging to develop, felt that the development of such a tool along with a strong strategy for physician education, would be helpful.

6 Patient Perspective Systematic Review

Summary

- One study on patient perspectives of using CT to diagnose pulmonary embolism was identified
- This study found that one-third of patients would prefer to forgo CT testing for a number of reasons including risk of adverse events and exposure to radiation from CT technology
- This suggests that some patients screened using CT for possible pulmonary embolism, if informed of the risks and benefits, would forego screening.
- One study is not sufficient for robust conclusions to be drawn and more literature is needed.

6.1 Objective

To determine patient's perspectives on the use of CT for diagnosing PE

6.2 Methods

A systematic review was completed. EMBASE, Medline, all EMB reviews, and PsychINFO were searched from inception until February 2nd, 2017. Terms aimed at capturing technology such as "computed tomography," "CT," "CTPA," and "CT pulmonary angiography" were combined using the Boolean Operator "or." These terms were then combined, using the Boolean Operator "and" with terms describing the patient experience, such as "attitudes," "perceptions," and "patient preference." No filters were applied. Details of this search can be found in Appendix B.

All abstracts were screened in duplicate. Abstracts proceeded to full-text review if: they examined patient perspectives or experiences with CT to diagnose PE, included only adults 18 years and older, reported any outcome, and was written in English or French. Abstracts were excluded if they failed to meet any of the above inclusion criteria, or if they: were animal models, or did not report original data. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in Table 10. Full-text review was completed in duplicate. Any discrepancy between reviewers was resolved through discussion and consensus.

Table 10. Inclusion and Exclusion Criteria for Systematic Review

Inclusion Criteria	Exclusions Criteria
• Examines patient perspective on using CT to diagnose PE • Adults over 18 years' old • Any outcome • English or French language only	• Does not examine patient perspectives on using CT to diagnose PE • Under 18 years' old • Not written in English or French • Animal models • Does not report original data

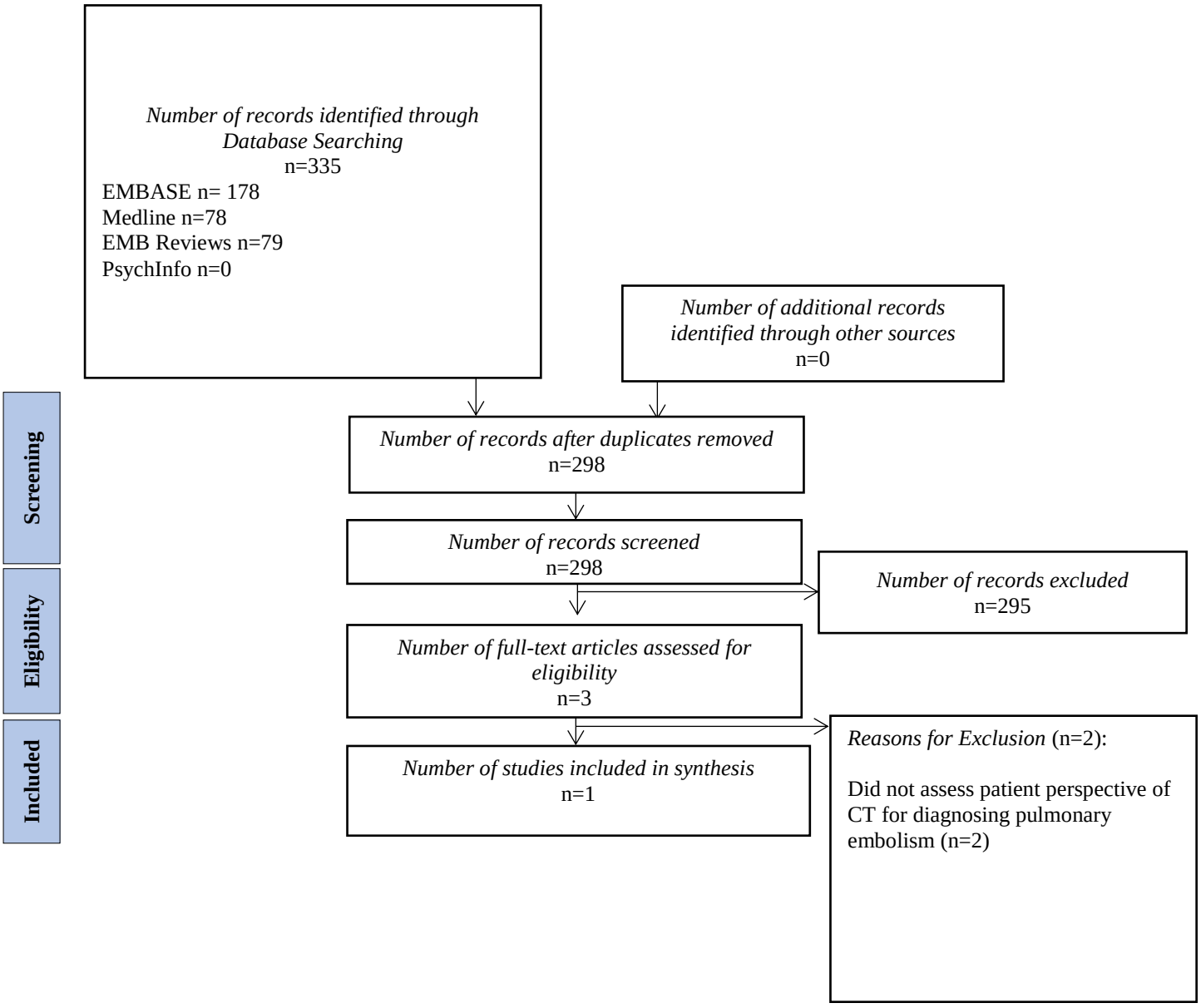
For all studies, year of publication, country, objective, methods, patient inclusion, patient demographics, outcomes measured, and key findings were extracted using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus.

During data extraction, quality assessment was completed in duplicate. Disagreement between reviewers was discussed and a consensus was reached. Studies were assessed using Downs and Blacks Checklist[121]. Using this checklist, each study was assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and power[121]. Studies are assigned a value of "1" if they meet the question criteria, "0" if they do not or if it is not possible to determine whether they meet the criteria; with one exception where one question may be given "2" points.

6.3 Results

335 citations were retrieved from EMBASE (n=178), PsychINFO (n=0), Medline (n=78) and all EMB Reviews (n=78). After duplicates were removed, 298 citations were reviewed. Two hundred and ninety-five were excluded, and three proceeded to full-text review. One study met the final inclusion criteria, and the remaining two were excluded (Figure 14).

Figure 14: Flow Chart



The included study was conducted by Geyer et al. in the United States and published in 2014[122] (Table 11). This study investigated the impact of shared decision making on testing strategies for PE. Two-hundred and three patients were included from the emergency department of an urban university hospital; these patients had a mean age of 55 years (SD: 17years), and 61% were male. Patients were included if they presented with chest pain or dyspnea, and were excluded if they were hemodynamically unstable or unable to participate due to altered mental status, intoxication or limited capacity to communicate in English.

Table 11: Summary of Included Study

Author, Year, Country	Objective and Methods	Clinical context	Participant Details	Key Findings	Quality Assessment
Greyer, 2014, United States	*Objective:* To determine patient preferences regarding PE diagnostic approach *Study Design:* Observational study *Methods:* Presentation of hypothetical scenario where patient has low pretest probability and elevated D-dimer. Patients asked to consider risks and benefits and express preference for imaging.	Emergency department of a urban university hospital	*Inclusion Criteria:* Patients presenting with chest pain or dyspnea *Exclusion Criteria:* hemodynamically unstable or unable to participate due to altered mental status, intoxication or limited capacity to communicate in English *Participant demographics*: 203 participants, mean age 55 years (SD: 17 years), 61% male	• 63% indicated a preference for CT in the above scenario, and 37% indicated a preference to not have a CT • All patients who had precious PE expressed preference for CT	20

CT: CT Pulmonary Angiography, SD: Standard Deviation

The risks and benefits of testing strategies were described to patients. Research staff presented patients with information on pretest probability assessment, D-dimer testing and CT pulmonary angiography. Patients were asked to consider a scenario where they had low pretest probability, but elevated D-dimer (between 500ng/mL and 1000ng/mL). Patients were also presented with 2 image arrays of 1000 other similar patients which displayed the risks of obtaining or declining a CT pulmonary angiography, including risks such as missed PE, adverse effects, false-positive.

Out of 203 participants, 63% indicated a preference for CT in the above scenario, and 37% indicated a preference to not have a CT. Patients who had previously had a PE were more likely to prefer CT (0% declined, p=0.07). Of patients who preferred not to have CT, 27% cited risk of malignancy due to radiation exposure, 24% cited risk of contrast-induced nephropathy, 3% cited risk of allergic reaction; the remaining patients declined due to a belief that the test was unnecessary. Of those who preferred CT testing, 85% worried that declining would result in

missing a PE diagnosis, and 15% were concerned about missing an alternate diagnosis discovered by CT.

6.4 Discussion

The literature on patient perspectives or preferences for PE testing is limited; only one study was identified in a systematic review of the literature. This study found that one-third of patients would prefer to forgo CT testing for a number of reasons including risk of adverse event and exposure to radiation from CT technology. This suggests that some patients may be screened using CT for possible PE, when, if informed of the risks and benefits, they would have forgone screening. One study is not sufficient for robust conclusions to be drawn and more literature is needed. However, this study suggests that some patients may have a preference for deferring CT testing.

7 Appropriate Use of CT

Summary

- 3,167 abstracts were reviewed, thirty-five full-texts were reviewed and fourteen studies were included.
- Two studies assessed the effectiveness of an audit and feedback system, five assessed the effectiveness of a clinical decision support (CDS), three assessed the effectiveness of a type of communication, three assessed the effectiveness of guidelines, and one assessed both a clinical decision support and guideline
- Pooled estimates obtained from the stratified meta-analysis suggest that only interventions involving clinical decision support tools were significantly effective on increasing CT yield.
- Barriers, such as time pressures and patient demands, as well as facilitators such as staff acceptance and buy-in, may change the success of the intervention.

7.1 Objective

To identify and determine the effectiveness of interventions to support appropriate use of CT for diagnosing PE

7.2 Methods

Search Strategy

A systematic review was completed. Medline, EMBASE, Cochrane Library, EconLit, and NHSEED were searched from inception until February 3, 2017. Terms aimed first at capturing the technology used in PE diagnosis, such as "CT scan," "tomography," "X-ray CT," "CAT scan," "multi-detector CT," or "CTPA." These terms were then combined, using the Boolean Operator "and" with terms describing the appropriate use of the technology, such as "decrease," "overuse," or "reduction." These terms were all further combined using Boolean Operator "and" with terms for the clinical condition, such as "pulmonary embolism" or "pulmonary thromboembolism." Results were limited to English or French language studies, and a second filter also excluded studies that were commentaries, editorials or conference proceedings. No other limitations or filters were applied. Details of this search can be found in Appendix C.

All abstracts were screened in duplicate. Abstracts proceeded to full-text review if: they assessed an intervention that ensured appropriate CT testing for diagnosing PE, included only adults over

18 years old, were a comparative study design, reported any outcome, and were written in English or French. Abstracts were excluded if they failed to meet any of the above inclusion criteria, or if they: were animal models, did not report original data, or were a commentary, editorial, or a conference proceeding. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in Table 12. Full-text review was completed in duplicate. Any discrepancy between reviewers was resolved through discussion and consensus.

Table 12. Inclusion and Exclusion Criteria for Systematic Review

Inclusion Criteria	**Exclusion Criteria**
• Study assesses intervention to ensure appropriate CT testing for diagnosing PE • Adults over 18 years' old • Must use a comparative study design to assess effectiveness or efficacy • Any outcome • English or French language only	• Does not apply a comparative study design • No intervention to ensure appropriate CT testing for PE • Under 18 years' old • Not written in English or French • Animal models • Does not report original data • Commentary, editorial, conference proceeding

For all studies, year of publication, country, objective, methods, clinical context, participant details, details of intervention, findings, and clinical pathway were extracted using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus.

The primary outcomes extracted during data extraction included: number of CT scans performed before and after the corresponding intervention, and CT yield. CT yield is the percentage of CT pulmonary angiographic examinations positive for acute PE and is therefore, a more accurate indicator to quantify the effect of an intervention on appropriate CT use.

During data extraction, quality assessment was completed in duplicate, with one reviewer doing primary data extraction and the other verifying data extraction. Disagreement between reviewers was discussed and a consensus was reached. Quality assessment was completed using Downs and Blacks Checklist[121]. Using this checklist, each study was assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and power[121]. Studies are assigned a value of "1" if they meet the question criteria, "0" if they do not or if it is not possible to determine whether they meet the criteria; with one exception where one question may be given "2" points.

A meta-analysis was conducted using the change in CT yield. A random effect model that assumes a normal distribution of effect size and different underlying effect for each study was used. *Cochran Q* and I^2 statistics were used to examine the heterogeneity of the included studies. All analyses were completed in R using R package *metafor* [123].

7.3 Results

4,571 citations were retrieved from EMBASE (n=2,779), Cochrane Library (n=70), Medline (n=1,722) and EconLit (n=3). After duplicates were removed, 3,167 citations were reviewed. 3,132 were excluded, and thirty-five proceeded to full-text review. Of these, fourteen studies were included.

7.3.1 Characteristics

The fourteen included studies were conducted between 2008 and 2016. Nine studies were from the U.S., two from Australia, one from the Netherlands, one from South Africa, and one from Spain. The number of participants who took part in the studies ranged significantly, from 21 physicians pre-intervention and 22 physicians post-intervention in the study by Raja et al.[124], to 46,834 patients pre-intervention and 49,673 patients post-intervention in the study by Geeting et al.[125]. Two studies assessed the effectiveness of an audit and feedback system [124,126], five assessed the effectiveness of a clinical decision support (CDS) [127-131], three assessed the effectiveness of a type of communication [132-134], three assessed the effectiveness of guidelines [135-137], and one assessed both a clinical decision support and guideline [125] (Table 15).

Figure 15. Flow Chart

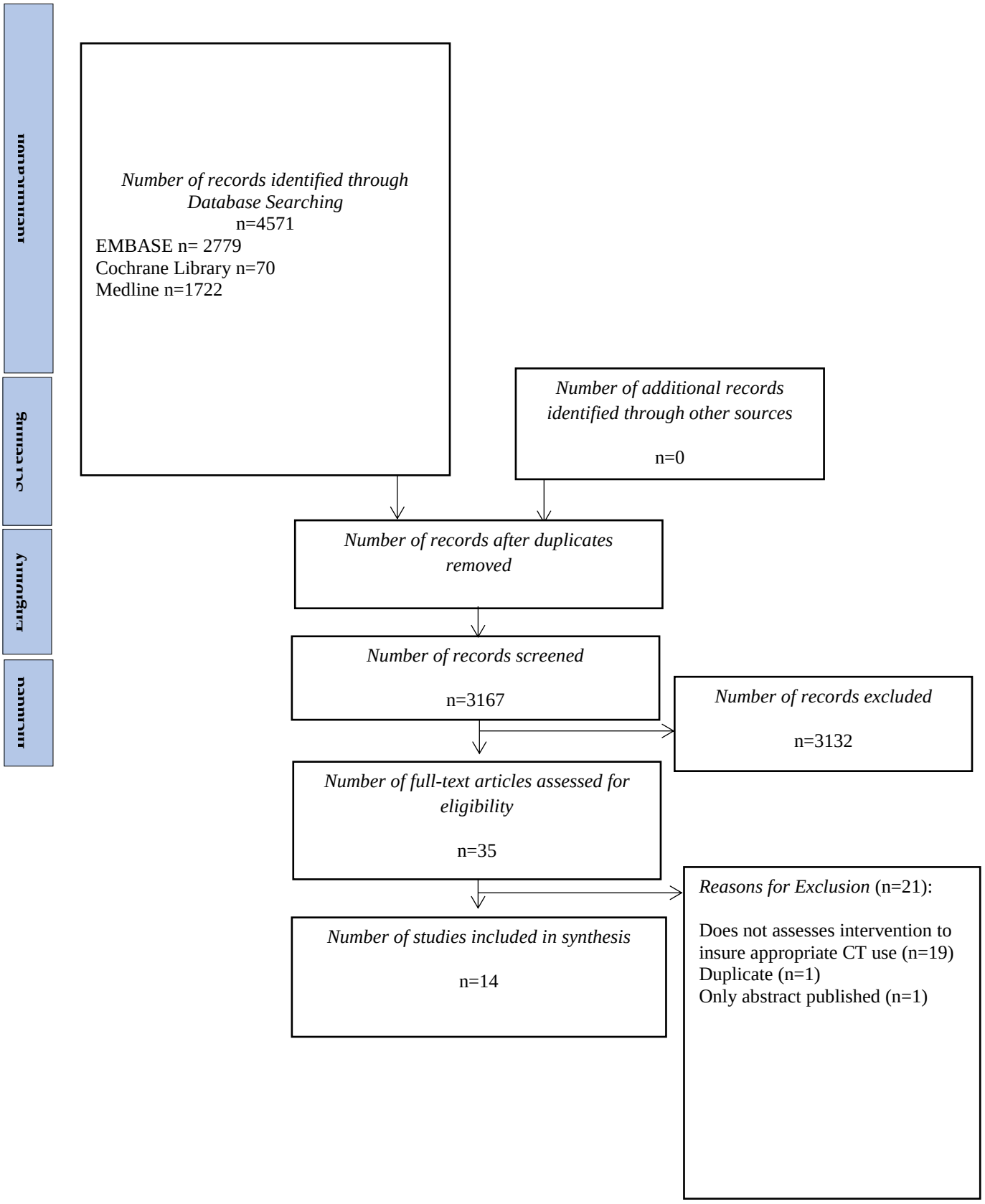


Table 13: Synthesis of Interventions

Study	Intervention	Description
AGARWAL[128]	CDS	Diagnostic imaging pathways online clinical decisions support tool, using Wells score as primary screening tool
BOOKER [126]	Audit and feedback	Presentation at monthly emergency department meeting. Individual utilization data was sent confidentially to each clinician/
DUNNE [127]	CDS	Clinical decision tool informed providers of the patient-specific pre-test probability for PE based on clinical suspicion and d-dimer results
GEETING[125]	CDS / Guidelines	Embedding a field for modified Wells score in the CTA order set. Modified wells score was required to order CT, but CT could be ordered regardless of score.
HARDIN [132]	Communication	Email sent to all Emergency Department physicians. Email reported that use of CT to diagnose PE was increasing, and that to prevent radiation exposure in young females, V/Q scan should be considered as an alternative method of diagnosis.
JIMENEZ 2015 [129]	CDS	Clinical Decision tool intended to guide diagnostic testing for PE. No other details reported.
KANAAN [133]	Communication	Formal educational intervention, consisting of a 45-minute didactic lecture followed by a 30-minute question and answer session.
MURTHY [136]	Guidelines / CDS	A PE diagnostic algorithm was distributed to all hospital clinicians, outlining the combined role of the validated modified Wells score and the quantitative D-dimer test in defining the pre-test probability of PE. Further, clinicians were prompted using a electronic CDS to enter the Wells score and the D-dimer test result, thereby defining the pre-test probability of PE.
ONG [135]	Guidelines	Using Wells score, patients were stratified into pre-test probability categories. Completion of the algorithm form was required before the CT radiographers would perform a CT.
PREVEDELLO [130]	CDS	Clinical decision support tool for PE-CT (based Wells criteria) within the institution's computerized physician order entry system. The clinical decision support required information about the level of clinical suspicion for PE and the serum D-dimer level).
RAJA [124]	Audit and feedback	Quarterly performance feedback reports sent via e-mail that displayed individual physicians' statistics and their performance compared with all emergency physicians.
RAJA [131]	CDS	Integration of clinical decision support using ED radiology computerized physician order entry system
STEIN [134]	Communication	Two hour-long seminars held with the available emergency department staff. Recommended that stable patients with a clinical suspicion of PE should initially be imaged with chest radiography.
WALEN [137]	Guidelines	Every physician requesting a CT for PE was asked to document Wells-scores on the request form and to document D-dimer.

CDS: Clinical Decision Support; CT: Computed Tomography pulmonary angiography; ED: Emergency Department; PE: pulmonary embolism

A diverse range of interventions to decrease CT use were used in these studies. The most common interventions involved the distribution of a PE diagnostic algorithm form (either physical or computerized) to all hospital clinicians that outlined the role of evidence-based

clinical decision support tools in the diagnosis of PE, such as the Wells score and D-dimer test. These forms prompted clinicians to enter scores for these decision support tools prior to entering a CT request.[127,129-131,135-137] Other common interventions were in-person education sessions that focused on clinical decision support tools such as the Wells criteria, PERC scores, and D-dimer testing [126,128,133] One study held educational seminars providing an algorithm that recommended imaging with chest radiography and V/Q scanning, to decrease the use of CT.[134] Another embedded a pre-test probability rule based on Wells criteria, which was required during the computerized physician order-entry process.[125] One study used a simple intervention of an email correspondence to all ED physicians that reported that the use of CT for PE was increasing, and that V/Q scans should be considered as an alternative method.[132] One study implemented emergency department physician performance feedback reports sent via email that displayed both individual physicians' statistics and their performance compared with anonymized results for the entire group of emergency physicians.[124]

Results from the included studies have been synthesized below. Detailed information on each study can be found in Appendix C.

7.3.2 Quality Assessment

The fourteen included studies had quality scores ranging from 9 [130] to 17 [138] out of 27. All studies had areas where quality was low or unclear. The three areas where quality was lowest was describing the principle confounders, randomization, and blinding. Since these studies were predominantly non-randomized controlled trials, using a pre- post-intervention design, these areas of low quality are predominantly related to limitations of the study design. Quality was high for the following elements: clearly describing the objective, clearly describing the main outcomes, valid and reliable outcome measures, and compliance with the intervention. The quality assessments of all included studies are synthesized in Table 14.

7.3.3 Meta-analysis

Included studies were divided into four groups based on intervention type: audit and feedback; clinical decision support; communication; and guidelines. Figure 16 summarizes the change in CT yield after intervention in each study and the pooled outcomes obtained by performing a

random effect meta-analysis stratified by the intervention type. All studies reported positive change of CT yield indicating that the interventions were effective on increasing CT yield. However, only three of them were statistically significant [130,136,137]. In all three studies, interventions involve using Well's score and D-dimer test results prior to the CT examination.

Table 14. Outcomes of Included Studies

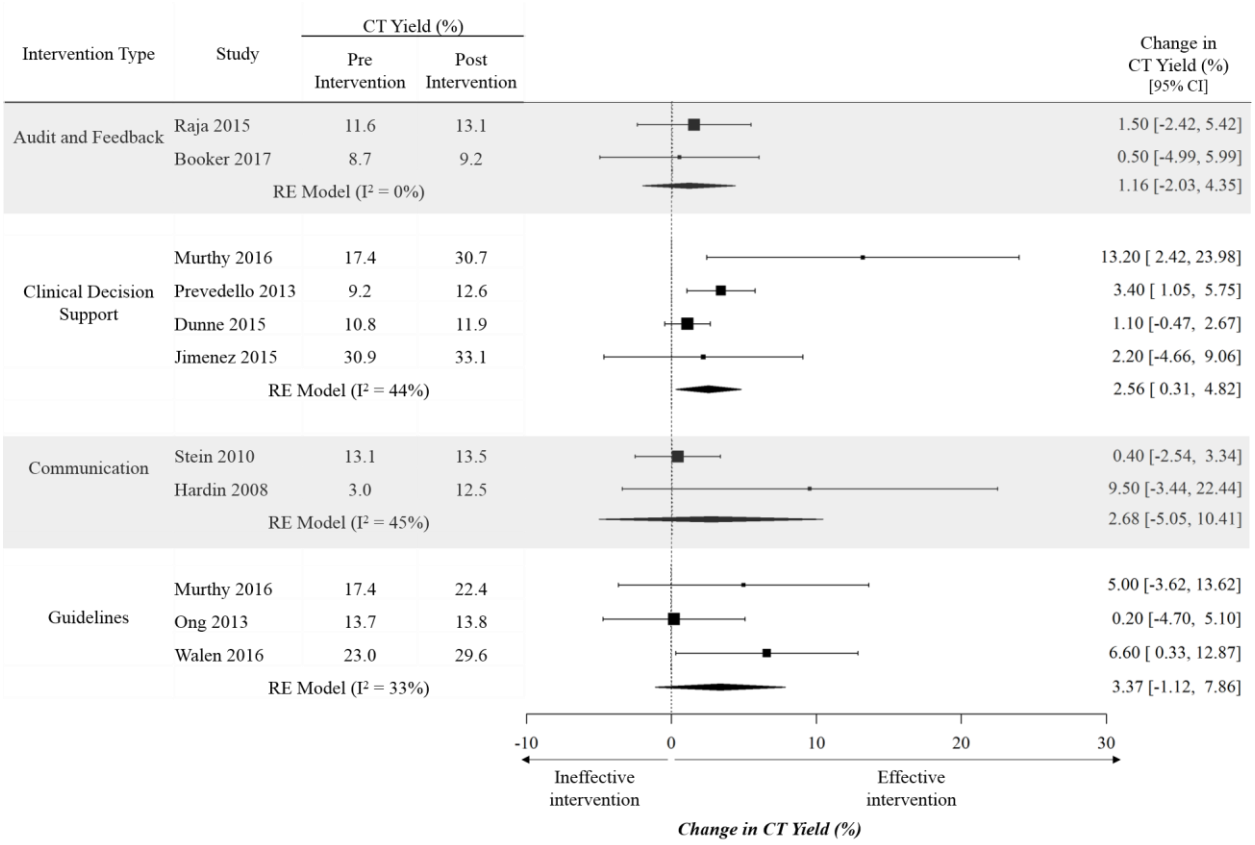
				CT Scans Ordered		**Effectiveness/Yield**	
Author, Year, Country	Pre-intervention Sample Size	Post-intervention Sample Size	Quality	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention
Audit and Feedback							
Booker	206	206	13	23	19	8.7%	9.2%
Raja	21 (Control)	22 (Intervention)	17	Control: 20.4 (per 1000 ED patients) Intervention: 20.2 (per 1000 ED patients)	Control: 20.1 (per 1000 ED patients) Intervention: 18.1 (per 1000 ED patients)	Control: 11.6% Intervention: 11.2%	Control: 11.2% Intervention: 13.1%
Clinical Decision Support							
Agarwal	187	109	16	NR	NR	NR	NR
Dunne	3037	2825	16	26.8 per 1000 admissions	22.6 per 1000 admissions*	10.4%	12.1%
Geetings	46,734	49,673	16	NR	1417	0.44%	0.38%
Jimenez	652	711	13	362	350	31%	33%
Prevedello	1542	1349	12	1542	1349	9.21%	12.60%*
Raja	3855	2983	11	NR	NR	NR	NR
Murthy	NR	NR	13	149	101	17.4%	31.7%*

Communication							
Hardin	33	32	15	33	32	3.03%	12.5%
Kanaan	100	100	14	NR	NR	NR	NR
Stein	1753	1843	12	1234	920	13.1%	13.5%
Guidelines							
Murthy	NR	NR	13	149	174	17.4%	22.4%
Ong	138	268	9	454	333	13.6%	13.8%
Walen	974	250	13	974	250	23%	29.6%*

ED: Emergency Department; NR: Not reported; OR: Odds Ratio; PE: pulmonary Embolism
*Statistically significant finding

There was no statistical evidence to conclude that the included studies in each intervention group were heterogeneous. Pooled estimates obtained from the stratified meta-analysis suggest that only interventions that involve clinical decision support tools were significantly effective on increasing CT yield.

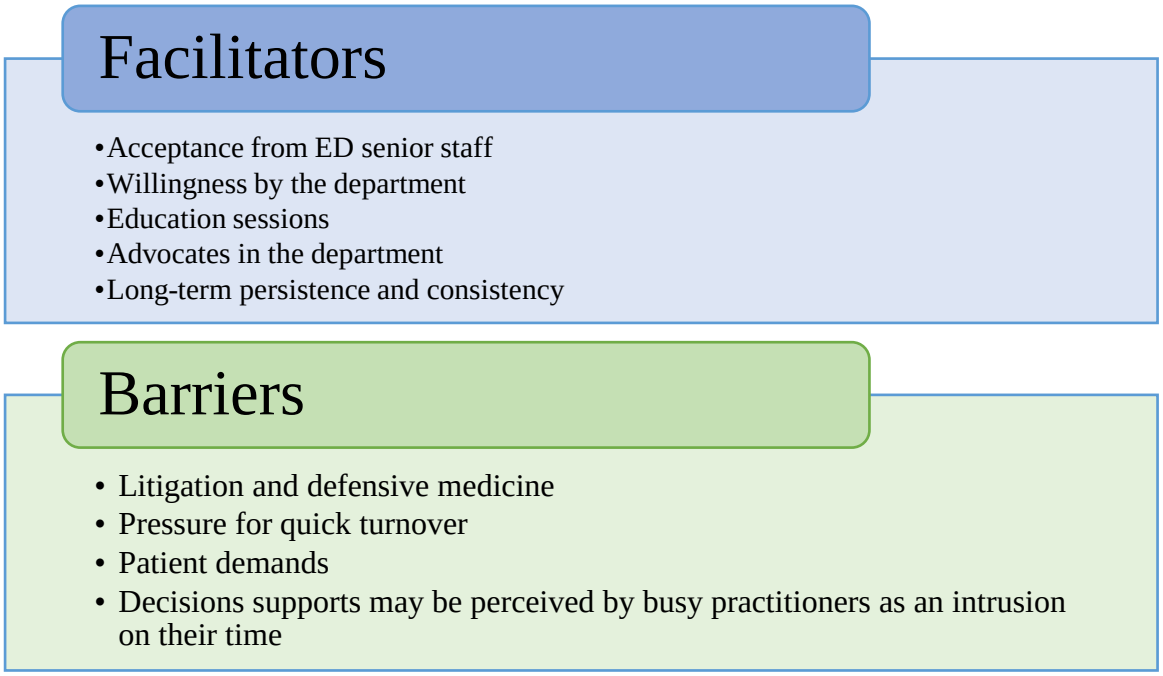
Figure 16: Forest plot of change in CT yield after intervention



7.3.4 Lessons Learned

The included studies identified a number of lessons learned, such as barriers, facilitators and impact of delivery mode (Figure 17). One study found that to be successful, a mandatory process requires acceptance from emergency department senior staff, willingness by the department, frequent education sessions for new staff, and review sessions for others, and advocates in the department to promote and police the intervention [128]. Additionally, the need for long-term persistence, and consistency to ensure uptake and appropriate application of the tool were highlighted [135].

Figure 17: Barriers and Facilitators to Acceptance of Intervention



Studies found that some barriers to success included: litigation and defensive medicine [126], pressure for quick turnover [126], patient demands [126], and lack of time [133]. Decisions supports may be perceived by busy practitioners as an intrusion on their time, and therefore, it was found to be important to have the appropriate clinical departments on board for any plans to institute a decision support system [133].

Two studies found that an education-only intervention, that was not related to any consequences for the physician resulted in heterogeneous acceptance of the tool [127,130]. Another study found that a tool required reminders and care suggestions to be effective; a passive, one-time intervention had no effect [132].

7.4 Discussion

Literature on effective interventions to align CT use with appropriate practice is substantial; however, it is also diverse and heterogeneous. Broad categories of interventions used to promote appropriate CT use include clinical decision support tools, audit and feedback, communication and guidelines. However, each intervention differed on elements such as delivery mode, whether or not it was mandatory, and whether there was reinforcement.

When considered separately, one of the clinical decision support studies [130] and two of the guideline studies[136,137] showed statistically significant improvement in CT yield. The guideline studies relied on decision tools such as Wells and PERC, and therefore, the effectiveness of this intervention could be linked to the effectiveness of these tools for ruling out PE in certain patient groups. Due to the small number of studies the pooled results for each category are uncertain.

The included studies were of low to moderate quality. All studies had areas where quality was low or unclear, and therefore all were at risk of bias. However, many of the study limitations included not blinding, and not randomizing participants, which was predominately a consequence of the non-randomized pre- post- intervention study designs used.

A number of barriers and facilitators were identified, and should be considered if implementing an intervention to align CT use with appropriate practice. Acceptance and buy-in from staff, including the department and the emergency staff, having advocates in the department and long-term persistence and consistency were all identified as factors that promote the success of an intervention. Barriers such as litigation and defensive medicine, time pressures, and patient demands were all highlighted by the included studies. Considering these barriers prior to implementation may help improve the success of an intervention.

In order to draw strong conclusions about the effectiveness of interventions to increase the appropriate use of CT, more literature is required. If additional literature were available, it would be possible to do a meta-analysis based on broader categories to see what type of intervention is most likely to be effective. In the absence of additional literature, interventions to increase the appropriate use of CT appear to be effective with guideline-based interventions that recommend the use of Wells' and D-dimer and clinical decision supports that implement the use of Wells' and D-dimer being the most likely to change CT yield.

8 Cost-effectiveness and Economic Impact

Summary

- A cost-effectiveness analysis and budget impact analysis incorporating diagnostic and treatment costs for PE was completed.
- In the base case, an intervention of Wells→PERC→D-dimer→CT had the lowest costs with a total of $1981 and effectiveness of 12.489 QALYs.
- Wells→D-dimer→CT (moderate and high) resulted in an ICUR of $30,000 per QALY

8.1 Objective

To determine the cost-effectiveness of an intervention to support appropriate use of CT in diagnosing PE in emergency departments in British Columbia.

8.2 Overview of Previous Studies

8.2.1 Methods

An update of a previously conducted systematic review by Raymakers et al. [139] of cost-effectiveness analyses of diagnostic strategies incorporating CT for PE was conducted. Raymakers et al. searched the published literature from 1990 to 2012. To leverage this work, a de novo search which captured literature from 2012 to March 10th, 2017 was conducted using the search strategy developed by Raymakers et al[139]. The original study searched: MEDLINE, EMBASE, Health Technology Assessments, NHS Economic Evaluation Database, and the Cochrane Central Register of Clinical Trials. The update search included only MEDLINE and NHS Economic Evaluation Database as the majority of evidence is captured with those two databases[140]. The search was developed in MEDLINE using MeSH (medical subject heading) terms and keywords for the concepts PE and diagnostic tests (scintigraphy, tomography, D-dimer, ultrasonography, angiography, clinical probability assessment). These concepts were combined using a Boolean operator AND; then the results were combined with an economic

evaluation filter[141]. The search strategy for the update are in Appendix D. No language restrictions or publication type were applied to the search.

8.2.1.1 Inclusion Criteria

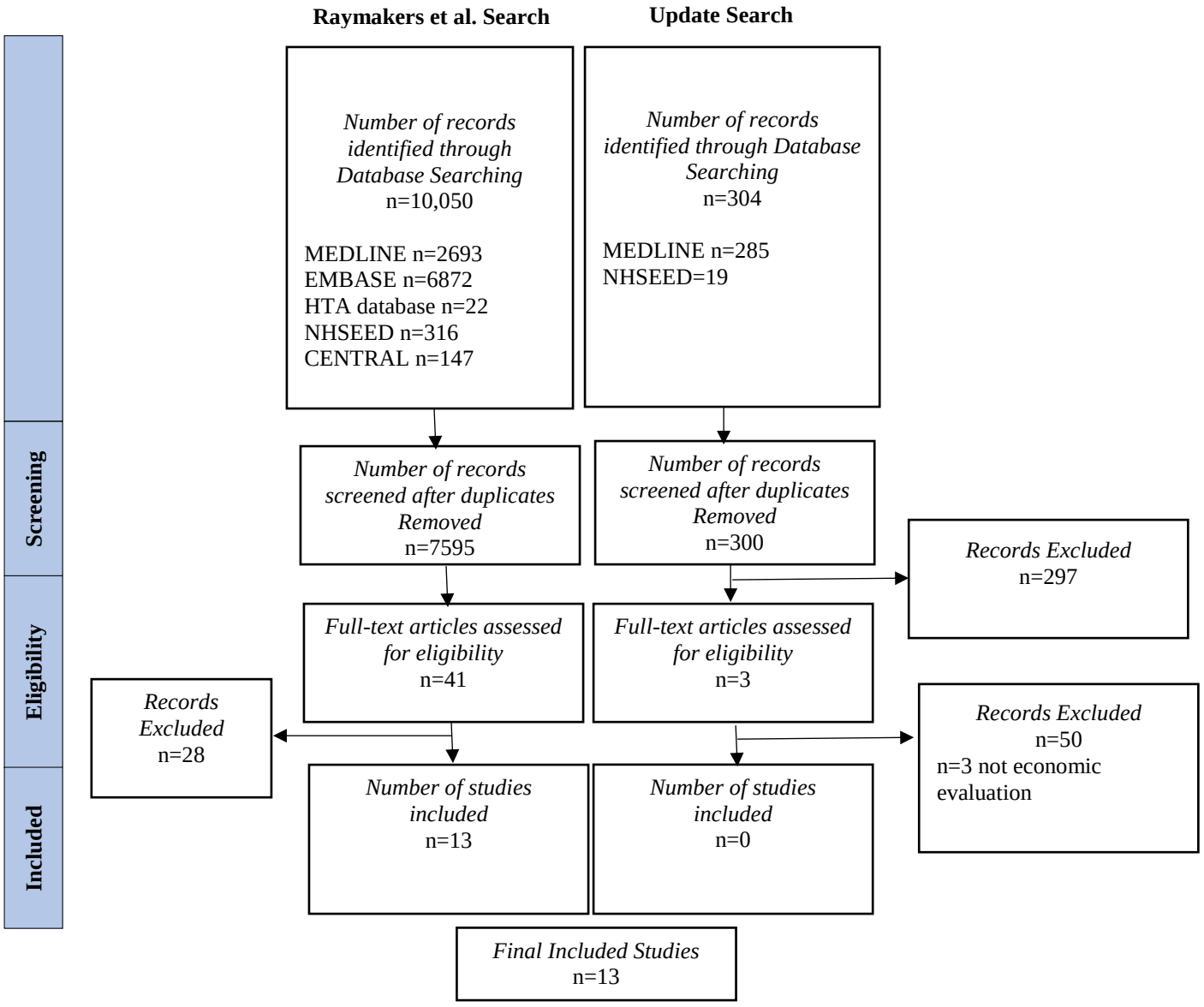
The abstracts were screened by a single reviewer, similar to the original review by Raymakers et al[139]. All abstracts selected for inclusion proceeded to full-text review. For inclusion in this update, a study had to meet the same inclusion criteria of the original systematic review: 1) report on a comparative economic evaluation of strategies for the diagnosis of PE; and 2) include CT as a component of at least one strategy. Data from the included studies were extracted using a standard data extraction form and narrative synthesis was used to summarize overall results of included studies.

8.2.2 Results

8.2.2.1 Identification of studies

A total of 300 citations were identified from the literature update search after removing duplicate records. Of those, 297 were excluded in the abstract review and 3 were included for the full-text analysis. In full-text review, all 3 were excluded from the final analysis. Thus, no new studies were identified in addition to the 13 studies reported in Raymakers et al.

Figure 18. Flow Chart of Review Process



8.2.2.2 Study characteristics

Individual characteristics of each economic evaluation have been previously reported by Raymakers et al[139]. Economic evaluations were conducted in Europe (n=6), USA (n=5), Canada (n=1), and Australia (n=1). The perspective of the cost-effectiveness analyses were mostly from a 3rd party payer perspective (n=5) or hospital perspective (n=3). Three studies measured effectiveness in quality-adjusted life years[142-144], with most studies measuring a form of survival. Time horizons reported included 3 months, one year, and lifetime. Almost all populations considered in economic evaluations were patients suspected of PE, one focused on pregnant women and another specifically on a high-risk population only[142,145]. All studies incorporated clinical probability assessment except for those populations already considered at a high-risk of PE (i.e. pregnant women).

Across all studies, the reported sensitivity of CT ranged from 0.70-0.955 and specificity of CT from 0.89-0.976. Costs in 2011 USD of CT scans ranged from $158.37 (Great Britain) - $840.89 (Switzerland). Cost sources included Medicare for those studies based in the USA, local hospitals (e.g., costs included physician fee, diagnostic, hospital stay, equipment, capital), and physician payment schedules.

8.2.2.3 Study results

A summary of the key results of the primary economic evaluations previously identified by Raymakers et al (n=13) are described in Table 15. The majority of studies reported CT as a component of their most cost-effective strategies, particularly after the use of D-dimer or in combination with ultrasound in their diagnostic strategy[145-151].

Overall, all economic evaluation studies incorporated clinical probability assessment (Wells Criteria or Geneva Score) into the diagnostic algorithms evaluated when populations were not previously risk stratified. The use of the more invasive test, pulmonary angiography, was not frequently evaluated as part of a diagnostic algorithm. CT was a component of most reported cost-effective diagnostic strategies, particularly after D-dimer or in combination with ultrasound. One study reported that CT alone was not cost-effective and should be considered with D-dimer and ultrasound [143], they reported D-dimer + compression US was the most cost-effective strategy. Another study reported V/Q + US + PA as the most cost-effective strategy compared with CT-based strategies[152].

Table 15. Summary of previously published cost-effectiveness analyses

First Author Year	Location	Objective	Comparators	Results	Conclusion
Doyle 2004[145]	USA	A cost analysis to evaluate which of several diagnostic strategies was the most CE with the least number of deaths from PE	• CUS • V/Q scan • hCT	hCT as the initial diagnostic regimen was found to be the most CE at $17,208 per life saved	Spiral CT offers the most CE method
Duriseti 2006[144]	USA	To examine the cost-effectiveness of a quantitative D-dimer assay for the evaluation of patients with suspected PE in an urban ED	Combinations of: • CUS • V/Q • CTA • CTP	CTP without D-dimer was the preferred strategy. CUS-V/Q scanning was always dominated by CT-based strategies	When CTA is available, even the most sensitive D-dimer assay is not likely to be cost-effective.
Duriseti 2010[143]	USA	To evaluates the cost-effectiveness of different diagnostic strategies in an ED for patients presenting with undifferentiated symptoms suggestive of PE	Combinations of: • D-dimer • CTP • CTV • V/Q • CUS	For all patient pretest categories, the most cost-effective diagnostic strategy is to use an initial ELISA D-dimer test, followed by CUS of the lower extremities if the D-dimer is above a specified cutoff	Using ELISA D-dimer assay (at cutoffs higher than currently used) followed by CUS, can reduce costs and improve outcomes
Larcos 2000[152]	Australia	To compare the cost-effectiveness of alternative methods of diagnosing acute PE	• V/Q + US + PA • CT + US + PA CT	V/Q is both more expensive and more effective than CT alone, resulting in 20.1 additional lives saved at a cost of $940 per life year gained	Incremental cost-effectiveness of the V/Q based strategy over CT is reasonable in comparison with other health interventions.
Lee 2011[151]	USA	To evaluate cost-effectiveness of diagnostic strategies for PE in patients with a high, intermediate, or low clinical	• V/Q + PA • CT • US + CT	D-dimer ± CT was more effective and less costly than CT alone in the	The strategy of D-dimer followed by CT was the cost-effective option in

		probability of PE	• CT + US • D-dimer + CT • D-dimer + US + CT • D-dimer + CT + US • V/Q + CT • D-dimer + V/Q + PA	intermediate and high probability populations.	populations with low, intermediate and high probabilities of PE.
Paterson 2001[150]	Canada	To assess the cost-effectiveness of hCT for the diagnosis of acute PE	Combinations of: • V/Q • Leg US • hCT • Conventional PA	Cost per additional life saved was $70,833 for hCT ± leg US relative to V/Q ± leg US ± hCT.	hCT can replace PA in patient with non-diagnostic V/Q scan and negative leg US findings.
Perrier 2003[147]	Switzerland	Evaluate the most CE strategy for the three levels of clinical probability of PE	Combinations of: • hCT • D-dimer • US • V/Q scan • Angiography	For low clinical probability, the most CE strategy was D-dimer, US, and V/Q. For intermediate and high clinical probability, a fourth test must be added, either CT or angiography	hCT in diagnostic strategies for PE is CE provided that it is combined with D-dimer and US, in contrast, hCT as a single-test is not CE
Righini 2007[146]	Switzerland	To evaluate the cost-effectiveness of including D-dimer and CUS in the workup of PE, with particular attention to patient age	• CP ± D-dimer ± CUS ± hCT • CP ± D-dimer ± hCT • CP ± CUS ± hCT • hCT alone	D-dimer measurement was highly cost-saving under the age of 80 years; above 80 years, the cost-sparing effect of D-dimer was diminished	Diagnostic strategies using D-dimer was less expensive; CUS is costly, and only marginally improves the safety of diagnostic strategies for PE
Van Erkel 1996[148]	Western Europe	To investigate the cost-effectiveness of diagnostic strategies involving hCT or conventional PA in the diagnosis of suspected PE	Combinations of: • V/Q scan • US • D-dimer • Conventional PA • hCT	All the best strategies included hCT	Use of hCT angiography is likely to reduce the mortality and improve cost-effectiveness in the diagnostic work-up of suspected PE
Van Erkel	The Netherlands	Re-examine the CEA previously conducted to adjust for updated	Combinations of: • V/Q scan	Strategies including hCT had lower costs and	Confirms results of the original CEA

1998[149]		information	• US • D-dimer • PA • hCT	higher survival than strategies using PA	
Van Erkel 1999[153]	France, the Netherlands, Great Britain, Austria, Switzerland, USA	To assess whether potential differences in costs for diagnostic procedures and treatment of PE among European and U. S. hospitals alter the optimal CE diagnostic strategy for PE	• CT strategies (CT, US, P-scan, V/Q, D-Dimer) • PA strategies (US, PA, V/Q, D-dimer) • Reference strategies (no therapy, all therapy)	There were considerable differences in costs for diagnostic and therapeutic procedures for PE among the participating centers. These differences, however, did not affect the most CE strategy based on incremental cost-effectiveness.	In all hospitals, the most CE strategy appeared to be US followed by hCT.
Ward 2011[142]	USA	To analyze the cost-effectiveness of a selective CT strategy incorporating the use of CUS to diagnosis and treat DVT in patients with a high pretest probability of PE	• Universal CT • Selective CT with screening CUS	The selective CT strategy cost $1,457.70 less than the universal CT strategy and resulted in a gain of 0.0213 quality-adjusted life years	A selective CT strategy using CUS is CE for patients provided they have a high pretest probability of PE

CE = cost-effective; CP = clinical probability; CT = computed tomography; CTA = computed tomography angiogram; CTP = computed tomography with pulmonary portion; CTV = computed tomography venography; CUS = compression ultrasonography; ED = emergency department; hCT = helical computed tomography; P-scan = perfusion scan; PA = pulmonary angiography; PE = pulmonary embolism; US = lower limb venous ultrasound; V/Q = ventilation-perfusion

*Unable to access full-text of Elias 2004[154]

8.3 Methods

8.3.1 Objective

The objective of the economic evaluation was to evaluate the lifetime costs, health outcomes and the cost-effectiveness of interventions to promote the appropriate use of CT in diagnosing PE in emergency departments of British Columbia.

8.3.2 Type of analysis

A cost-utility analysis was conducted to account for the broad set of clinical outcomes associated with a correct diagnosis or misdiagnosis of PE. Health outcomes were expressed as quality adjusted life years (QALYs) to capture both the mortality and morbidity impacts related to the condition and its treatments. The primary outcome in the economic analysis was the incremental cost per QALY gained (commonly referred to as the incremental cost-utility ratio [ICUR]).

8.3.3 Target population and settings

The target population was adults suspected of first-time PE presenting at the emergency department. All patients were suspected of PE based on clinical judgment by the attending physician prior to any clinical decision rule and/or diagnostic imaging. Patients with a history of PE were not included given that these patients have a higher risk of PE recurrence and represent a different population. The reference case cohort represents patients 65 years of age with 50% males; this matched the population of those diagnosed with PE in British Columbia in 2014/15. The underlying prevalence of PE was estimated to be 9.25%, this prevalence was estimated from patients with suspected PE in the emergency departments at four tertiary care hospitals in Canada.[155]

Not all patients suspected of PE may be suitable to undergo CT. Specifically, pregnant patients may undergo thoracic ultrasound and were not considered in this analysis. Lastly, the setting was the British Columbia health care system in which it is assumed that there was access to all diagnostic tests (e.g., biochemical d-dimer test and CT).

8.3.4 Time horizon and discount rate

As the clinical and cost consequences of a diagnosis of PE can persist indefinitely, a lifetime time horizon was adopted. Alternative time horizons were evaluated in sensitivity analyses (i.e., three months, one year). The current revised draft Canadian guidelines suggests a discount rate

of 1.5% per annum[156]. In the base case analysis the costs and benefits were discounted at 1.5%, and a sensitivity analysis was conducted with the previously recommended discount rate of 5%[157].

8.3.5 Diagnostic algorithm comparators

As noted in the clinical review, diagnosis of PE may involve a multistep sequential algorithm. Previous algorithms have included clinical decision support tools (such as Wells' score or PERC), ancillary test (such as D-dimer) and diagnostic imaging (usually CT). Integrated approaches combining a sequence of diagnostic tests and using well-validated algorithms have been proposed[158]. Clinical guidelines have also recommended different algorithms. In the Clinical Practice Guidelines, algorithms including Wells' and D-dimer are recommended; in Calgary the PERC is also included.

Thus, the model considers 5 different comparators:

1. CT alone

   All patients suspected of PE have a CT scan
2. D-dimer→CT

   All patients suspected of PE have a D-dimer test, negative tests are no longer suspected and positive tests go on to CT
3. Wells→D-dimer→CT (high)

   All patients who have a **high** Wells' score go directly to CT, all patients with a **moderate or low** Wells' score have D-dimer, and positive D-dimer go to CT
4. Wells→D-dimer→CT (moderate and high)

   All patients who have a **high or moderate** Wells' score go directly to CT, all patients with a **low** Wells' score have D-dimer, and positive D-dimer go to CT
5. Wells→PERC→D-dimer→CT

   All patients who have a high Wells' score go directly to CT, all patients with a moderate Wells' score have D-dimer and positive D-dimer go to CT, all patients with a low Wells' score have a PERC test, negative PERC tests are no longer suspected of PE, positive PERC tests have D-Dimer and positive D-Dimer go to CT

In the appropriate use of CT section (Appropriate Use of CT) four types of interventions are identified: clinical decision support; audit and feedback; guidelines, and communication. Most of these interventions include the use of a PE diagnostic algorithm such as the Wells' score and D-dimer test. All four types of interventions report a positive change to CT yield, suggesting that these interventions are effective at increasing CT yield compared to CT alone. Of the three studies that demonstrate statistically significant results, the interventions include Wells' score and D-dimer tests prior to the CT examination [130,136,137]. However, yield alone is not sufficient to maximize the health benefits of patients. Improving yield may result in fewer patients being diagnosed, and therefore, patients missing treatment. Thus it is important to understand how different diagnostic algorithms affect the diagnostic accuracy and how changes in accuracy affect patients' health and system costs. Based on those interventions deemed to improve yield and the jurisdictional scan, the economic model explores strategies incorporating clinical decision support tools with different combinations of the Wells' Score, PERC and D-dimer test prior to CT for diagnosing PE. Guidelines, audit and feedback and communication are not explicitly considered in the model. The audit and feedback intervention requires electronic medical records which are not currently available across BC and would incur high costs for little benefit. The guideline and communication strategy rely on having a more cost-effective strategy to communicate. The model estimates which strategy would be the most cost-effective to help determine which strategy to develop guidelines or communication interventions.

Ancillary tests such as leg ultrasound or capnography[5] were not identified to be used in British Columbia from the jurisdictional scan and thus were not considered in the intervention strategy. A variety of imaging modalities can be used to diagnose PE (CT, MRI, V/Q-based technologies, thoracic ultrasound), however, these tests were not considered as they are rarely used in BC practice.

8.3.6 Perspective

The perspective of the British Columbia Ministry of Health was adopted. As such, all medical costs were captured including the cost of laboratory and diagnostic tests, emergency visits, in-patient visits and medical services. Indirect non-medical costs, such as productivity losses and out-of-pocket costs, were not considered in this analysis.

[5] The monitoring of carbon dioxide in exhaled air.

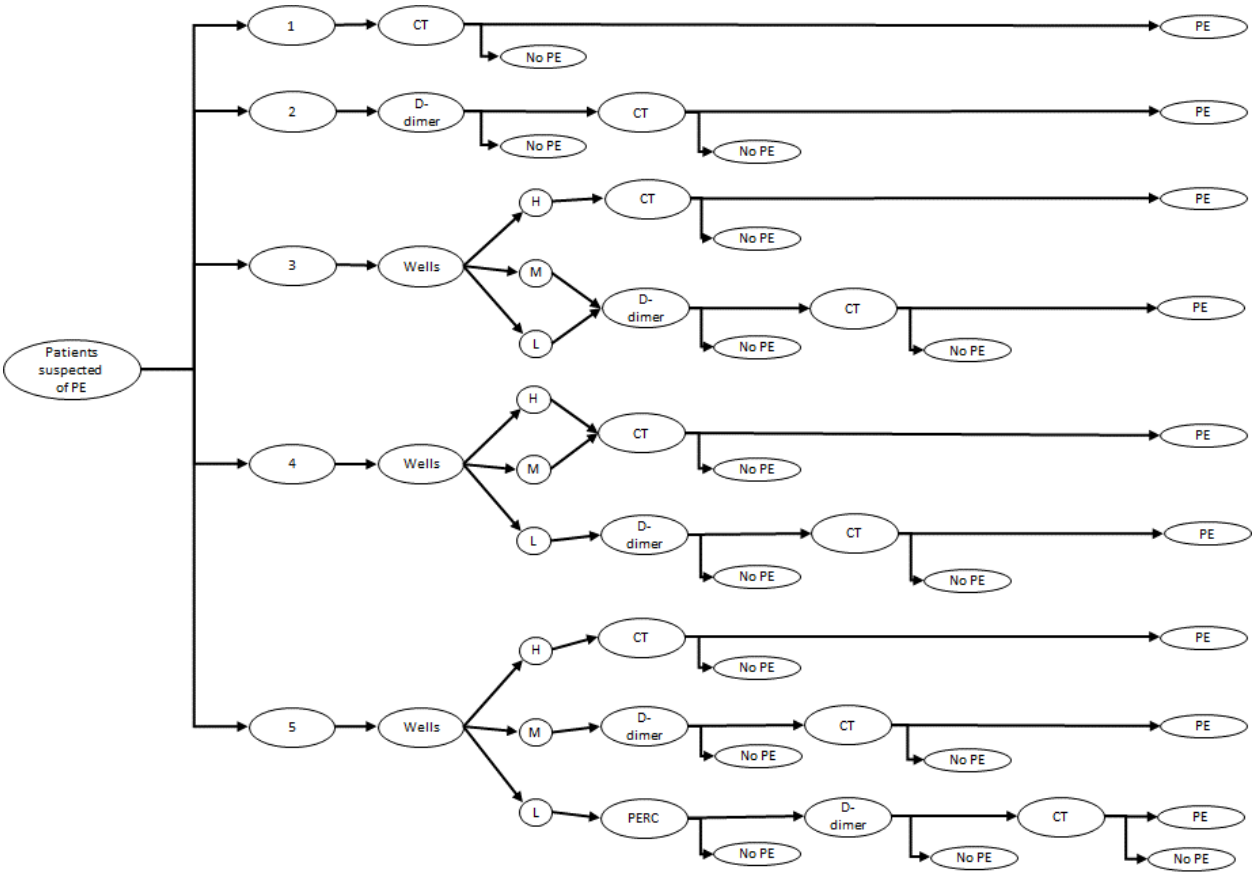
8.3.7 Decision analytic model

A decision-analytic hybrid model was constructed to examine the clinical outcomes and costs associated with diagnostic algorithms in a cohort of patients suspected of PE. The model was developed in collaboration with CADTH. Conceptualization was undertaken by CADTH and the HTA Unit in collaboration with clinical experts, CADTH programmed the model, the HTA Unit validated the programming and populated the model inputs for this version of the model.

The model consisted of i) an upfront decision tree that captured the short-term screening outcomes and ii) a downstream Markov model to capture the long-term outcomes following a correct or mis-diagnosis. The Markov model was previously developed to assess anti-coagulant treatment on deep vein thrombosis (DVT) and PE[99]. The model was updated to be relevant to PE only by eliminating the DVT specifics outcomes. The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature, and the model conceptualization was subsequently validated by clinical experts from different medical specialties who are involved at different stages of the diagnostic process and clinical management of PE (i.e., radiology, emergency medicine).

Figure 19 presents the structure of the decision tree reflecting the diagnostic process for PE (i.e., diagnostic algorithm of sequential tests). The patient cohort, patients suspected of PE, proceed through the decision tree. Depending on which of the 5 diagnostic pathways were being tested patients are tested with either CT, D-dimer or Wells. Follow-up testing depended on the diagnostic pathway.

Figure 19. Decision Tree for Diagnostic Algorithms

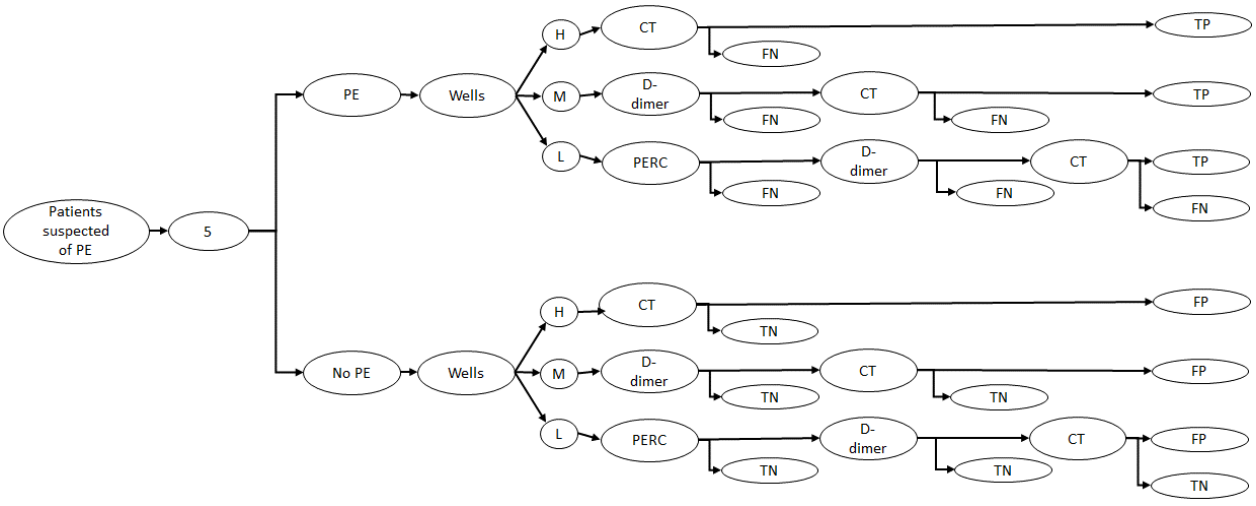


CT=computed tomography; H= high; M=moderate; L=low; PE = pulmonary embolism, 1= CT alone, 2= D-dimer→CT, 3= Wells→D-dimer→CT (high), 4= Wells→D-dimer→CT (moderate and high), 5= Wells→PERC→D-dimer→CT

Using the prevalence and sensitivity and specificity of each test, patients were identified as having 'PE' or 'No PE'. The model also identified the proportion of those identified as having PE as true positive or false positive and the proportion of those identified as No PE as true negatives or false negatives. This is important for the second part of the model since patients were treated based on how they are identified and patient outcomes depend on the treatment they received and whether they were identified correctly.

Figure 20 demonstrates an example of one comparator and how prevalence and accuracy data are used to estimate the outcomes of the decision tree i.e. true positive, true negative, false positive and false negative.

Figure 20. Decision Tree Outcomes for Algorithm: Wells→PERC→D-dimer→CT

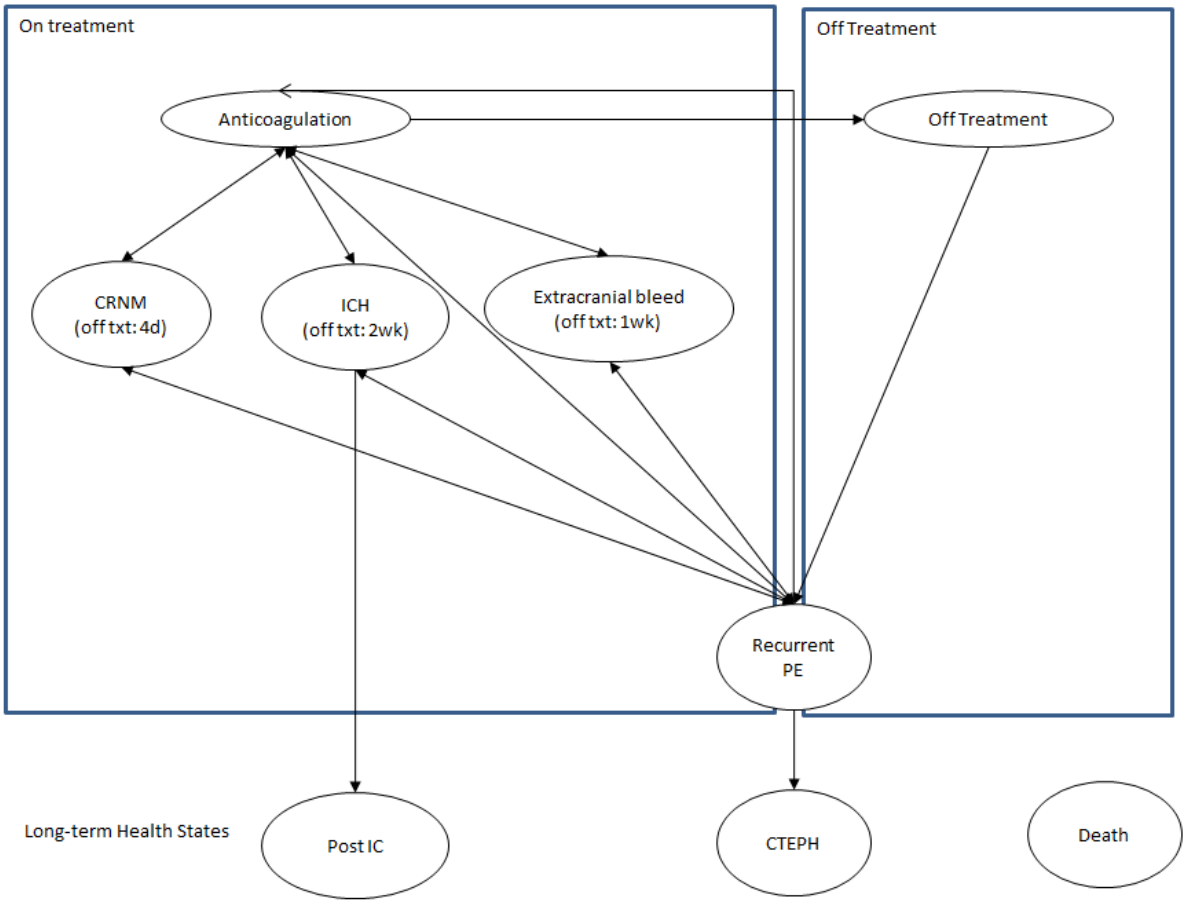


CT=computed tomography; H= high; M=moderate; L=low; PE = pulmonary embolism, 1= CT alone, 2= D-dimer→CT, 3= Wells→D-dimer→CT (high), 4= Wells→D-dimer→CT (moderate and high), 5= Wells→PERC→D-dimer→CT

Outputs of the decision tree, relating to diagnostic test accuracy (i.e., true positive, false positive, true negative, false negative), were incorporated into the adapted Markov cohort model (Figure 21).

From the decision tree, patients classified as true positives entered the treatment model. While on treatment, patients were at risk of treatment-related complications but also benefit from treatment due to a lowered risk of recurrent PE. Patients classified as true negatives did not receive treatment and were not at risk of any recurrent PE. Patients classified as false positives inappropriately received treatment and were at risk of treatment-related complications during the treatment period without any treatment-related benefits (i.e., they were not at risk of recurrent PE). Patients classified as false negative, on the contrary, are modelled to have treatment withheld and were at an increased risk of recurrent PE and PE-related mortality. Patients that had a second non-fatal PE were assumed to be correctly diagnosed and anticoagulant therapy initiated.

Figure 21. Conceptual Design of the Markov component of the economic model



After each cycle, patients may move from one health state to the next as indicated by the arrows or remain in the previous state. Although not explicitly shown, all states can lead to death. Adapted from CADTH, 2016[99]

ICH = intracranial hemorrhage, CRNM = clinically relevant non-major; CTEPH = chronic thromboembolic pulmonary hypertension; PTS = post-thrombotic syndrome; VTE = venous thromboembolism

The Markov portion of the model adopted a lifetime perspective that follows patients to death. At any health state in the model, patients had a risk of death. Patients diagnosed with PE entered the "anticoagulation state" while patients not diagnosed with PE entered the "off treatment" state. Patients cycled monthly through health states related to PE and its treatment, including:

- **Recurrent PE[159]:** PE that occurs after successful treatment of newly diagnosed PE (successful treatment where there is clear clinical improvement of patient symptoms and signs within the first 2 weeks of treatment)

- **Major bleeds (intracranial, extracranial)[160]:** major bleeding includes bleeding into a critical area or organ, intracranial (intracerebral, subdural) and extracranial (gastrointestinal, non-gastrointestinal) bleeding were considered
- **Clinically relevant non-major bleeds[161]:** an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but requires clinical response, in that it leads to at least one of the following (a hospital admission for bleeding, or a physician guided medical/surgical treatment for bleeding, or change in therapy which could include interruption or discontinuation)
- **Chronic thromboembolic pulmonary hypertension[162]:** chronic obstruction of pulmonary artery branches following PE
- **Post-intracranial bleed:** long-term complications following diagnosis and treatment of an intracranial bleed

In the reference case, the initial duration of treatment was three months and patients are treated indefinitely if they had a recurrent PE. Further details relating to this model have been published elsewhere[99].

The decision analytic model was constructed in Microsoft Excel.

8.3.8 Model Inputs

8.3.8.1 Inputs for the Diagnostic decision tree

The clinical review provided inputs on the diagnostic test accuracy of CT which was subsequently incorporated into the decision tree. Sixteen studies with a total sample size of 2,670 (range 48 – 773) were included in the meta-analysis using a bivariate mixed effects model. The pooled estimated diagnostic values of CT for sensitivity was 84.8% (81.7% - 87.5%) and for specificity was 93.0% (90.9% - 94.6%).

The proportion of patients categorized as low, moderate, and high risk by Wells' Score was taken from the literature, the pretest probability was low in 734 patients (3.4% with PE), moderate in 403 (27.8% with PE), and high in 102 (78.4% with PE)[46]. Diagnostic accuracy of D-dimer testing was taken from a previously published meta-analysis which reported a 95.0% (90.0% - 98.0%) pooled estimate of sensitivity and 45.0% (38.0% - 52.0%) specificity[163].

Diagnostic accuracy of PERC was also taken from a previously published meta-analysis which reported a pooled estimate of 97.0% (96.0% - 98.0%) sensitivity and a specificity of 23.0% (22.0% to 24.0%)[164].

The probability of having PE, if suspected of PE, used in the model was 9.25%. This was estimated from 930 patients with suspected PE in emergency departments at four tertiary care hospitals in Canada.[155]

8.3.8.2 Inputs for the Treatment Markov model

Baseline probabilities in the re-adapted Markov model are outlined in Table 16. Specifically, false positive patients entered the anticoagulant health state and were assumed to receive a course of treatment for three months. Their risks of experiencing a bleeding adverse event during the treatment period was increased to the same levels as true positives although their probability of a recurrent PE was set to zero. After treatment ends, the prognosis of false positive patients was modelled to be similar to the general population who did not have a prior PE diagnosis. False negative patients were at an increased risk of death and an increased risk of recurrent PE in the first month given that treatment was withheld (Table 16). Thereafter, the prognosis of these patients in terms of their risk of mortality and recurrence was assumed to be similar to PE patients off anticoagulant treatment (i.e., risks are higher than the general population but lower than those with an incident PE). True negatives were modelled to reflect a general Canadian population with general Canadian mortality rates applied.

Table 16. Baseline probabilities of recurrent PE.

Parameter		Value (probabilistic)	References
Recurrent PE	**On Treatment**		
	3-month probability of recurrent PE (short-term LMWH+VKA)†	0.017 (Beta: α= 14; β=811)	Quinlan, 2004[165]
	Annual probability of recurrent PE (lifetime LMWH+VKA)₮	0.031 (Normal: μ=0.031; σ=0.012)	Agnelli, 2003[16]
	Off Treatment/ Untreated		
	First month probability of recurrent PE	0.263 (Beta: α= 5; β=14)	Barritt, 1960[166]
	Annual probability of recurrent PE	0.041 (Normal: μ=0.041; σ=0.009)	Agnelli, 2003[16]
Treatment-related bleeds	**On Treatment**		
	3-month probability of major bleed (short-term LMWH+VKA)	0.014 (Beta: α= 14; β=1,009)	Quinlan, 2004[165]
	6-month probability of CRNM bleed (short-term LMWH+VKA)	0.082 (Beta: α= 1,111; β=12,452)	CADTH, 2016[99]
	Annual probability of major bleed (lifetime LMWH/VKA)	0.027 (Normal: μ= 0.012; σ= 0.010)	Aujesky, 2005[167]
PE-related mortality*	**On Treatment**		
	Case fatality rate, treated±	0.6 (Beta: α= 23,040; β=288,580)	Stein, 2012[168]
	Probability of death (short-term, month 2 to 3)	0.008 (Normal: μ=0.008; σ=0.0005)	Wells, 2016[169]
	Probability of death (long-term, >3 months)	0.033 (Beta: α= 125; β=153)	Schulman, 2006[170]
	Off Treatment		
	Case fatality rate, untreated±	0.263 (Beta: α= 5; β=14)	Barritt, 1960[166]

CRNM = clinically relevant non-major bleed; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist
† Applies for the first six months of the model
₮ Applies from the seventh month onwards
±Applied to the cycle of an incident PE
*After PE, mortality rates return to the Canadian general population age-specific mortality rate.

8.3.9 Utilities

Given that the diagnosis of PE occurs rapidly (within hours/days), no utility weights were applied to outcomes associated with the diagnostic decision tree. Utility weights were applied to each health state in the treatment Markov model. The length of utility impact was assumed to be one month for PE, one week for major extracranial bleed, and permanent for both major intracranial bleeds and CTEPH. Table 17 summarizes the utility values, a more detailed description is available in the original treatment model[99].

Utility values for PE, extracranial bleed, and major intracranial bleed were based on thrombosis clinic patients (n=215) with a history of lower limb DVT or PE in Ottawa, Ontario, Canada[171].

The utility values for PE was 0.75, extracranial bleed was 0.65, and major intracranial bleed was 0.15. The utility value for post intracranial bleed was 0.713 and was based on a population in the United Kingdom. The utility value for CTEPH was 0.648 and based on 15 patients with CTEPH in Spain. The majority of the utility values for health states in the treatment model were determined through the standard gamble method although post intracranial bleed and CTEPH are from a generic (i.e., EQ-5D) and disease-specific quality of life scale (i.e., Cambridge Pulmonary Hypertension Outcomes Review), respectively. Age-specific Canadian population norms were applied for patients not experiencing an acute event or long-term consequences of a disease/treatment-related event. These were from the general population (n=1,555) in Canada with health status measured using EQ-5D to estimate preference weights for population utility values[172].

Table 17. Utility values for treatment-related health states

Parameter	Description	Utility value (probabilistic)	Reference
Population norm	General population (n=1,555); EQ-5D Canada	Age 55-64: 0.828 (Beta: α= 657.74; β=136.63) Age 65-75: 0.79 (Beta: α= 535.88; β=142.45) Age 75+: 0.705 (Beta: α= 463.41; β=193.91)	Johnson [172]
PE EC bleed Major IC bleed	Lower extremity DVT or PE patients (n=215); standard gamble Canada	0.75 (Beta: α= 161.25; β=53.75) 0.65 (Beta: α= 139.75; β=75.25) 0.15 (Beta: α= 32.25; β=182.75)	Hogg, 2013[171]
Post IC bleed	Population-based cohort (n=2,425); EQ-5D UK	0.713 (Beta: α= 1,729.03; β=695.98)	Rivero-Arias, 2010[173]
CTEPH	CTEPH patients (n=15); EQ-5D Spain	0.648 (Beta: α= 9.72; β=5.28)	Roman, 2013[174]
Death		0	Assumption

PE = pulmonary embolism; EC = extracranial; IC = intracranial; CTEPH = chronic thromboembolic pulmonary hypertension

8.3.10 Costs

Given the model's perspective (i.e., public health care payer), only direct medical costs were considered. Whenever possible, the most current BC cost estimates were used. If BC costs were unavailable, costs are estimated from the literature were used. Where costs were unavailable from Canada conversion of currency was conducted using the Bank of Canada currency converter[175]. All cost estimates reflected 2016/2017 Canadian dollar and, if necessary, prices

were adjusted to 2016 values using the health care component of the consumer price index inflation calculator from the Bank of Canada[176].

Resources with equal utilization across all diagnostic strategies (i.e., initial physician clinical examination) were omitted from the analysis. Similarly, given that symptoms of PE may be undifferentiated, costs of other tests performed for differential diagnosis purposes unrelated to PE (e.g., chest X-ray, ECG) were considered outside of the scope of this study's interest.

8.3.10.1 Program Costs for Implementation of Clinical Decision Support Tool

The cost of implementing the clinical decision support tool was based on the costs from the University of Calgary's Clinical Research Unit in designing a clinical decision support tool for PE which included the development process and linking the tools to a database for data collection[177]. Costs for maintenance of the tool were also obtained from the University of Calgary. The cost of implementation of an online-based clinical decision support tool in Calgary was estimated to be $30,000 with annual maintenance costs of $5,000.

8.3.10.2 Per patient diagnostic test costs

8.3.10.2.1 Risk Stratification with Wells' Score and PERC

In order to calculate the cost per patient for the clinical decision support tool program (implementation and annual costs), the number of patients eligible for assessment (those suspected of PE in British Columbia) must be established. Data from CIHI suggests that for all of British Columbia, there were 1,477,564 ED visits in 2014/2015[178]. An audit of CTs for diagnosing PE was conducted in Fraser Health Authority in 2012/2013 over a 1.5 year period[179]. In this audit, it was reported for 850,000 ED visits in the Fraser Health Authority, 3,555 CT examinations for PE were performed which gives an estimate of 4.18 CT examinations for PE per 1,000 ED visits. It has also been reported that the Fraser Health Authority covers 1.8 million of 4.631 million residents in British Columbia (39%)[180]. Using these estimates, the number of patients suspected of PE in British Columbia and eligible for diagnostic imaging by CT were calculated:

- 3,555 CT examinations over 1.5 years provides an estimate of 2,370 per year. Assuming 2,370 CT scans represents 39% of all CT scans in British Columbia, then this would suggest 6,097 examinations for PE.
- Applying the estimate of 4.18 CT examinations for PE per 1,000 ED visits to the total number of 1,477,564 ED visits in 2014/2015 for all of British Columbia, this would suggest 6,180 examinations for PE.

Given the estimates of 6,097 to 6,180 examinations for PE, the decision analytic model assumed that approximately 6,139 CT examinations for PE are performed each year. Thus the cost per patient for the clinical decision support tool program for patients assessed by the Wells' Score was averaged over 6,139 patients suspected of PE in British Columbia.

In addition to costing the clinical decision support tool program over all patients assessed by the Wells' Score, the cost of emergency physician time to complete the clinical score was incorporated. The time to complete the Wells' Score was based on expert opinion (five minutes), this value was slightly lower than previously reported (10 minutes, range of 5 – 15)[181]. However, in British Columbia, the physician fee for an emergency department consultation is not time-dependent; the length of an emergency department consultation is variable and based on several factors reflective of patient characteristics and available hospital resources. As the average length of a consultation is unknown, the review assumed the consultation rate of an emergency department consultation ($128.34) was per hour. Based on a completion time of five minutes for the Wells' score and the cost per hour for an emergency consultation of $128.34, the total cost of completing the Wells' Score was estimated to be $10.70. Taking into consideration the cost of the clinical decision support tool, the total cost per patient for the Wells' Score was $12.49. To estimate the cost of assessing PERC after Wells', it is assumed that the cost of implementation and maintenance of a clinical decision support tool is already incorporated into the Wells' Score, thus the additional cost of PERC is only the time cost of completing PERC. The total cost per patient for the PERC score was $10.70 (

Table 18).

8.3.10.2.2 Laboratory and imaging *tests (D-Dimer and CT)*

Laboratory and diagnostic costs included both the tests and the physician's charge for interpretation of the test. Physician billing were obtained from the British Columbia Ministry of Health Medical Services Commission Payment Schedule. The physician cost of a D-dimer test was $23.59. The physician cost of a CT was $98.38 and the cost of a CT test was $725. The cost of a CT test was based on data provided by the British Columbia Ministry of Health.

Table 18. Per patient costs

Risk stratification and tests	**Parameter**		**Value**	**Reference(s)**	**Total cost per patient**
Wells Score	Clinical decision support tool	Cases of suspected PE	6,139	Calculated	**$12.49**
		Lifetime, years	5	Assumption	
		Implementation. cost	$30,000	University of Calgary[177]	
		Annual maintenance. cost	$5,000	University of Calgary[177]	
		Clinical decision support tool, cost per patient^	$1.79	Calculated	
	Completion of Wells' Score	Time, minutes (range)	5 (0-15)	Expert opinion, NICE[181]	
		Emergency physician consultation, cost	$128.34	BC Schedule of Fees[182]	
		Completion of Wells' Score, cost per patient	$10.70	Calculated	
PERC	Completion of PERC Score		$10.70	Calculated	**$10.70**
D-Dimer	D-Dimer Physician Fee		$23.59	BC Schedule of Fees[182]	**$23.59**
CT	CT Physician Fee		$98.39	BC Schedule of Fees[182]	**$823.38**
	CT Imaging Test		$725	BC Ministry of Health	

^Completion time by emergency physician assumed to be equivalent to Wells' Score; [&]CT Physician Fee + CT Imaging Test
PE = pulmonary embolism; Pulmonary Embolism Rule-out Criteria; CT = computed tomography

8.3.10.3 Treatment Costs

The treatment costs of patients with positive test results for PE included: anticoagulation therapy, laboratory tests, and physician fees. The standard of care for patients diagnosed with PE was initial parenteral anticoagulation (i.e., LMWH) followed by at least three-months of oral administration of VKAs which was overlapped with LMWH until systemic anticoagulation is achieved. Given the findings of the recently published Markov model suggesting that this treatment regimen remains the most likely cost-effective intervention[99], treatment in the reference case was assumed to be this regimen. VKA requires monitoring of INR and dose titration. The resources relating to laboratory tests for monitoring anticoagulant therapy was based on the existing published Markov model [99].

Drug costs were determined using the British Columbia Pharmacare Formulary[183]. No additional markup or dispensing fee was applied.

Table 19. Anticoagulation treatment costs

Treatment	Details	Costs	Monthly Costs				References
Low-molecular Weight Heparin (LMWH)	LMWH for 7 days + Nursing Time	LMWH: $23.8212 / day Nursing Time: $12.51	$179.26				BC Ministry of Health, CADTH [99]
Vitamin K antagonist (VKA)	Daily Warfarin	$0.0715 / day[%]	$2.17			Total Costs: Months 0-3: $47.75 Months 4-6: 27.23 Months 6+: 10.53	BC PharmaCare Formulary Search[183]
	Test / Interpretation		Month				
			0-3	4-6	6+		
	INR test # of INR Tests: Months 0-3: 8 Months 4-6: 3 Months 6+: 1	$12.31 / test	$32.83	$12.31	$4.10		BC Schedule of Fees[182]
	INR and VKA Interpretation # of Interpretations: Months 0-3: 3 Months 4-6: 3 Months 6+: 1	$12.75 / interpretation	$12.75	$12.75	$4.25		Ontario Schedule of Benefits[184]

INR = international normalized ratio

8.3.10.4 Event Costs

Costs to manage PE and treatment-related complications were based on the published Markov model (Table 20)[99]. The cost of PE management reflected a weighted cost based on an assumption that 67% are in an inpatient setting while the remaining are in an outpatient service. To estimate the costs of PE treated as an inpatient, the length of stay was assumed to be 7.8 days[99]. This length of stay was used in the previously published model and was very similar to the 7.5 days estimated using BC-based data. The resource use of treating PE in an outpatient setting were the same as those previously used[99]. These costs included consultations with an

emergency physician, a general practitioner, a specialist and blood counts.[99]. Descriptions of other event costs are detailed in Table 20.

As British Columbia specific costs were not available for treatment of PE, the Ontario Case Costing Initiative provided hospital-related costs (i.e., length of hospitalization, nursing, in-hospital pharmacy costs and overhead costs). The British Columbia Ministry of Health Medical Services Commission Payment Schedule provided the physician billing fees for associated visits. These sources provided estimates of event costs for PE (inpatient and outpatient), CRNM bleeds, and EC bleeds. Estimates of resource use and costs for IC bleeds, CTEPH, and post-IC bleeds were derived from the literature[99]. The cost of an intracranial bleed used in the previously published model was very similar to the $17,044 estimated using BC-based data.

Table 20. Event costs

Parameter	Components Included	Total Cost	Source
PE (inpatient)	PE as most responsible diagnosis (7.8 day LOS): $7054[99] Specialist Consultation: $169.06/visit Specialist Follow-up: $80.39/visit	$8038.29	BC Schedule of Fees[182],
PE (outpatient)	ER Visit: $399[99] ER Consultation: $128.34/visit GP Consultation: $82.24/visit Specialist Consultation: $169.06/visit Specialist Follow-up: $80.39/visit Blood Count: $5.77/test	$956.59	BC Schedule of Fees[182]
CRNM Bleed	ER Visit: $285[99] ER Consultation: $128.34/visit	$417.36	BC Schedule of Fees[182]
EC Bleed	Cost of GI hemorrhage treatment[99]	$5591.79	BC Schedule of Fees[182]
IC Bleed	Acute treatment cost of hemorrhagic stroke which included initial hospitalization and follow-up costs	$17,531.90	Goeree, 2005[185]
CTEPH	PTE surgery was assumed in 56.8% of patients	$47,867.86	Rubens, 2007[186]
Post-IC Bleed	Yearly cost (adjusted to monthly costs for one-month follow-up): $8,243	$696.61	Wells 2012[187]

PE = pulmonary embolism; LOS = length of stay; ER = emergency room; GP = general practitioner; GI = gastrointestinal; CRNM = clinically relevant non-major; EC = extracranial; IC = intracranial; CTEPH = chronic thromboembolic pulmonary hypertension; PTE = pulmonary thromboendarterectomy

8.3.11 Model Validation

The model structure and data inputs were presented to two Canadian clinical experts to ensure that the model, its parameters and its assumptions reflected Canadian clinical practice and the

available body of literature (face validity). Internal validity was assessed by ensuring the mathematical calculations were performed correctly and were consistent with the model specification. Logical discrepancies were assessed by evaluating it under hypothetical and extreme conditions. The model also underwent external peer review.

The long-term component i.e. Markov model also underwent external validation[99]. However, given that the model was restructured for a slightly different application, further external validation was conducted to ensure the revised model remained valid. Validation was done independently by comparing rates of recurrent PE and death reported in other studies[188]. To externally validate the decision tree, the model's outputs in terms of diagnostic accuracy (i.e., true positive, true negatives, false positive, false negatives) were compared to positive CT yield established by the audit of CTs in diagnosing PE in the Fraser Health Authority, the yield reported at Vancouver General Hospital and Richmond Hospital[189] and interventions identified in the clinical review (Appropriate Use of CT)[190].

8.3.12 Sensitivity Analysis

Sensitivity analyses were conducted to evaluate the degree to which the uncertainty in cost and effectiveness parameters impacted the models' findings. Sensitivity analyses were conducted to explore situations in which the results would change and to characterize the impact of different model assumptions. These included:

- **Patient demographics:** The reference case represents the demographics of patients with newly diagnosed PE in British Columbia, the population of patients suspected with PE may differ and thus the age and proportion male were varied.
- **Time horizon:** The reference case presented the lifetime cost-effectiveness of strategies. Given that the long-term outcomes are based on extrapolation, shorter model durations were explored (3 month, 1 year).
- **Discount rate:** The reference case adopted the most recent discount rate recommendation of 1.5%, the previously recommended discount rate of 5% was explored.
- **Prevalence of PE among suspected PE:** The reference case model assumed the general population suspected of PE reported in Canadian studies. However, some patients are at increased risk of PE and thus this parameter was varied.

- **Cost of clinical decision support tool:** Cost of implementation of the electronic clinical decision support tool may vary for hospitals and regional health authorities. Sensitivity analysis tested implementation costs of half and double the base case cost.
- **Time to complete Wells' Score:** The reference case assumed the time for an emergency physician to complete the Wells' Score was 5 minutes, a range of 0-15 minutes was explored.

8.3.13 Probabilistic Sensitivity Analysis

The reference case findings for the economic evaluations reflect the deterministic results; probabilistic results were based on 2,500 Monte Carlo simulations of the parameters' distributions. For the simulation, probability distributions related to natural history, resource utilization, costs and utilities were incorporated into the analysis, adopting standard methods for defining parameter uncertainty. Risk stratification and diagnostic accuracy were characterized by beta distributions, treatment effects were characterized by normal or beta distributions, transition probabilities and relative risks were characterized by beta and normal distributions, utility values were characterized by beta distributions, and event costs were characterized by gamma distributions. To account for the correlation between sensitivity and specificity of the diagnostic accuracy of CT, 5,000 paired values of sensitivity and specificity were generated based on the empirical correlation structure. The probabilistic results characterize the extent to which parameter uncertainty impacts the cost-effectiveness estimates in the model. Results of the probabilistic analysis are presented on a cost-effectiveness acceptability curve (CEAC). This graph presents the probability that each strategy is optimal given different willingness-to-pay values for an additional QALY gained.

8.4 Results

8.4.1 Model Validation

For external validation, the model's outputs were compared to independent clinical studies. The current economic model was meant to reflect the general Canadian population, therefore, the model's predictions on mortality are compared to those reported in registry and cohort studies.

Table 21. Results of model validation exercise

Parameter	Study	Reported Results (95%CI)	Model Prediction
All-cause mortality	Lobo, 2006[191] *Registry of 4,145 patients* *Age NR; 43.0% males* *Setting: Spain* *Total follow up: 3 months after hospital discharge*	**Cumulative Mortality** 3 months: 5.07%	**Cumulative Mortality** 3 months: 7.87%
	Pengo, 2006[13] *Case study involving 223 patients* *Age 60.8; 42.2% males* *[treatment for minimum of 6 months and extended based on individuals]* *Setting: Italy* *Total follow up: 10 years*	**Cumulative Mortality** 3 months: 10.3% (6.3 to 14.4) 1 year: 13.4% (8.9 to 17.9) 10 years: 25.1% (14.2 to 36)	**Cumulative Mortality [in true positive cohort]** 3 months: 7.87% 1 year: 9.19% 10 years: 20.04%
Major bleeding	Lobo, 2006[191]	**Cumulative Incidence** 3 months: 1.39%	**Cumulative Incidence** 3 months: 1.34%
Recurrent PE	Lobo, 2006[191]	**Cumulative Incidence** 3 months: 1.71%	**Cumulative Incidence:** 3 months: 1.62%
Recurrent PE	Pengo, 2006[13]	**Cumulative Incidence** 3 months: 4.9% (1.9 to 7.9) 1 year: 8.0% (4.2 to 11.8) 10 years: 29.1% (16.9 to 41.3)	**Cumulative Incidence** 3 months: 1.62% 1 year: 4.98% 10 years: 30.97%
CTEPH	Pengo, 2006[13]	**Cumulative Incidence** 6 months: 1.0% (8.1 to 17) 1 year: 3.1% (0.7 to 5.5) 2 years: 3.8% (1.1 to 6.5)	**Cumulative Incidence** 6 months: 0.003% 1 year: 0.005% 2 years: 0.008%

PE = pulmonary embolism; CTEPH = chronic thromboembolic pulmonary hypertension; CI = confidence interval; NR = not reported

At three months, post-diagnosis, the cumulative mortality rate has been reported to range from 5.07% to 10.3%[13,191]. The current model predicted 7.87%. Over a ten-year period, the model predictions were found to slightly underestimate mortality although it remained within the reported 95% confidence interval[13]. The model closely predicted the 3-month cumulative incidence of several clinical events reported by Lobo et al.[191], however, the model's predicted incidence of recurrent PE was lower than that of Pengo et al[13]. The only health outcome found to be very different was the cumulative incidence of CTEPH. The current model's prediction was nearly 100-fold lower than the reported incidence. The likely reason for this underestimation lied with the model structure, where it is assumed patients develop CTEPH only upon experiencing a recurrent PE. Given the low probability of developing PE (3.1%) and only about 3.46% of

patients have a recurrent PE by the sixth month, the incidence of CTEPH estimated in the model is 0.0009%. As CTEPH is a relatively rare complication, no further changes were made to the model structure to re-calibrate the model towards this clinical outcome. Rather, sensitivity analyses are conducted varying the parameter related to CTEPH to understand the robustness of the model's findings.

In the clinical review yields of CT prior to the use of intervention ranged from 3% to 30.9%. The interventions tested use a combination of a risk stratification (mostly Wells' Score), followed by rule-out with D-dimer testing, and diagnostic imaging of CT. The post-intervention yield ranged from 9.2% to 33.1%, suggesting a change in yield of 0.2 to 13.2%. This is compared to the model estimates of change in yield for the diagnostic comparators that incorporate risk stratification (Wells' Score, PERC, and/or D-Dimer) compared with CT alone. The change in yield estimated in the model ranges from 2.8% to 6.9%. This range is narrower than those reported in the literature.

The audit of CT in Fraser Health Authority suggested an overall yield of 6.91%[192]. The yield is the percentage of CT examinations that are positive for PE, whether true positive or false positive. There were approximately 40 CT examinations for each of ten sites. The yield ranges from 2.50-20.0% for the various hospitals in Fraser Health Authority. In a retrospective analysis of 1424 CT examinations by Woo et al. at Vancouver General Hospital and Richmond Hospital 188 (13.2%) cases of PE were diagnosed. In this study the yield for inpatients was 14.0% compared to 14.5% for emergency room patients and 6.8% for outpatients.[189] Non-BC studies of interventions for the appropriate use of CT reported a wide range of yields prior to the intervention (3.0-30.9%, Figure 16). In the economic model, the yield of CT alone was 14.2%, which was very similar to that reported by Woo et al. but more than double that reported by the Fraser Health Authority in 2012/2013. For the other comparators in the model beyond use of CT alone, the yield ranged from 17.0 to 21.1%. The low yield of Fraser Health Authority reflects actual clinical practice in BC, but should be considered with caution since it is a single, unpublished study. Despite the limitations of this data and incorporating the results from Woo et al., there does seem to be varying yield across hospitals in BC with some performing lower than what may be possible with additional risk stratification tools. The high yield for all diagnostic

strategies in the economic model may not reflect actual clinical practice but rather the ideal diagnostic work-up; especially given the diagnostic accuracy of Wells' Score, PERC, D-Dimer, and CT were based on combined observational and experimental published studies. Overall, yield is dependent on several factors including, the patient population and the context-specific diagnostic accuracy of tests. It is expected that the diagnostic accuracy of tests when they are not used in an experimental setting may be lower which may result in lower yields than those reported by the model.

The patient population suspected of PE was also important. The model assumes that 9.25% of patients with suspected PE will be diagnosed with PE, however, this is dependent on physicians' clinical judgment. In populations where the probability of being diagnosed with PE is lower than the yield will also be lower. The model parameters or structure were not changed to calibrate the model to match the yield reported by the Fraser Health Authority, instead the prevalence of PE was tested in the sensitivity analysis.

8.4.2 Base Case Results

Results of the base case analysis are presented in Table 22 and Figure 22 with disaggregated costs in

Table 23. The strategy with the lowest cost was Wells→PERC→D-dimer→CT with a total cost of $1981 and an effectiveness of 12.489 QALYs. Two strategies were excluded as potential preferred strategies: 1) D-dimer→CT was less effective and more expensive than Wells→PERC→D-dimer→CT and 2)Wells→D-dimer→CT (high) was also ruled out as another available strategy provided more benefit at a lower cost per benefit. The remaining strategies resulted in the following ICURs. Wells→D-dimer→CT (moderate and high) came to an ICUR of

$30,000 per QALY gained compared to the baseline strategy of Wells→PERC→D-dimer-→CT. CT alone resulted in an ICUR of $364,900 per QALY gained compared to Wells→D-dimer→CT (moderate and high). Overall, CT alone results in the highest total QALYs, as CT was more accurate at diagnosing PE than interventions with risk stratification. However, it was only marginally better than Wells→D-dimer→CT (moderate and high) with an incremental QALY gain of 0.001 (0.4 quality-adjusted days).

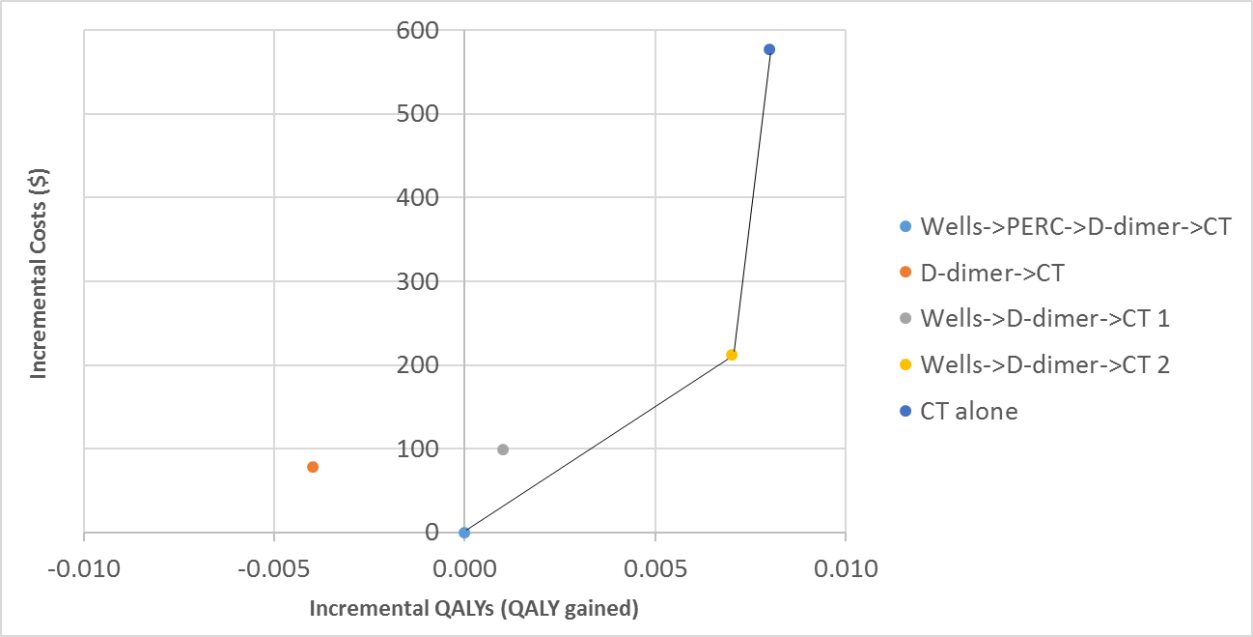
Table 22. Base case deterministic results – sequential ICUR

Strategy	Cost ($)	Incremental Cost	LYs	Incremental LYs	QALYs	Incremental QALYs	ICUR ($/QALY)
Wells→PERC→ D-dimer→CT	1981	0	16.68	-	12.489	-	-
D-dimer→CT	2059	78	16.67	-0.0048	12.485	-0.004	Dominated
Wells→D-dimer→CT (high)	2080	99	16.68	0.00098	12.490	0.001	Extendedly Dominated
Wells→D-dimer→CT (moderate and high)	2193	113	16.69	0.0080	12.496	0.006	30,300
CT alone	2558	365	16.69	0.0016	12.497	0.001	364,900

LY = life year; QALY = quality-adjusted life year; ICUR = incremental cost-utility ratio; PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography

In Figure 22, the incremental costs and effects from each intervention are presented. The connecting line represents the efficiency frontier, which links all strategies that are not dominated. The interventions not at the frontier (D-dimer→CT and Wells→D-dimer→CT (high) are not preferred since they provide the same or less benefit at a higher cost than the other interventions. The preferred strategy of the remaining interventions is dependent on the threshold or willingness-to-pay value for additional benefit (cost per QALY gained).

Figure 22. Incremental Cost-effectiveness Plane



W+P+DD+CT = Wells→PERC→D-dimer→CT; DD+CT = D-dimer→CT; W+DD+CT = Wells→D-dimer→CT (high); W+DD+CT2 = Wells→D-dimer→CT (moderate and high); CT = CT alone
QALY = quality-adjusted life year; CT = computed tomography

The CT alone strategy was associated with the greatest diagnostic and treatment costs, $823 and $1,738, respectively (

Table 23); all patients receive CT which is an expensive diagnostic imaging technique.

Furthermore, treatment costs were higher as there is the highest probability of all strategies to be

false positive (6.35%; other comparators ranged from 2.7% to 4.3%) and receive inappropriate treatment without any benefit. For other strategies, there were lower diagnostic costs (range from $440 to $617) given a lower proportion of patients were tested with CT as they underwent risk stratification (Wells', PERC, D-Dimer). Similarly, long-term costs related to treatment and complication with PE were lower compared with CT alone as less patients, correctly and mistakenly, underwent treatment for PE.

Table 23. Disaggregated Costs and Effectiveness

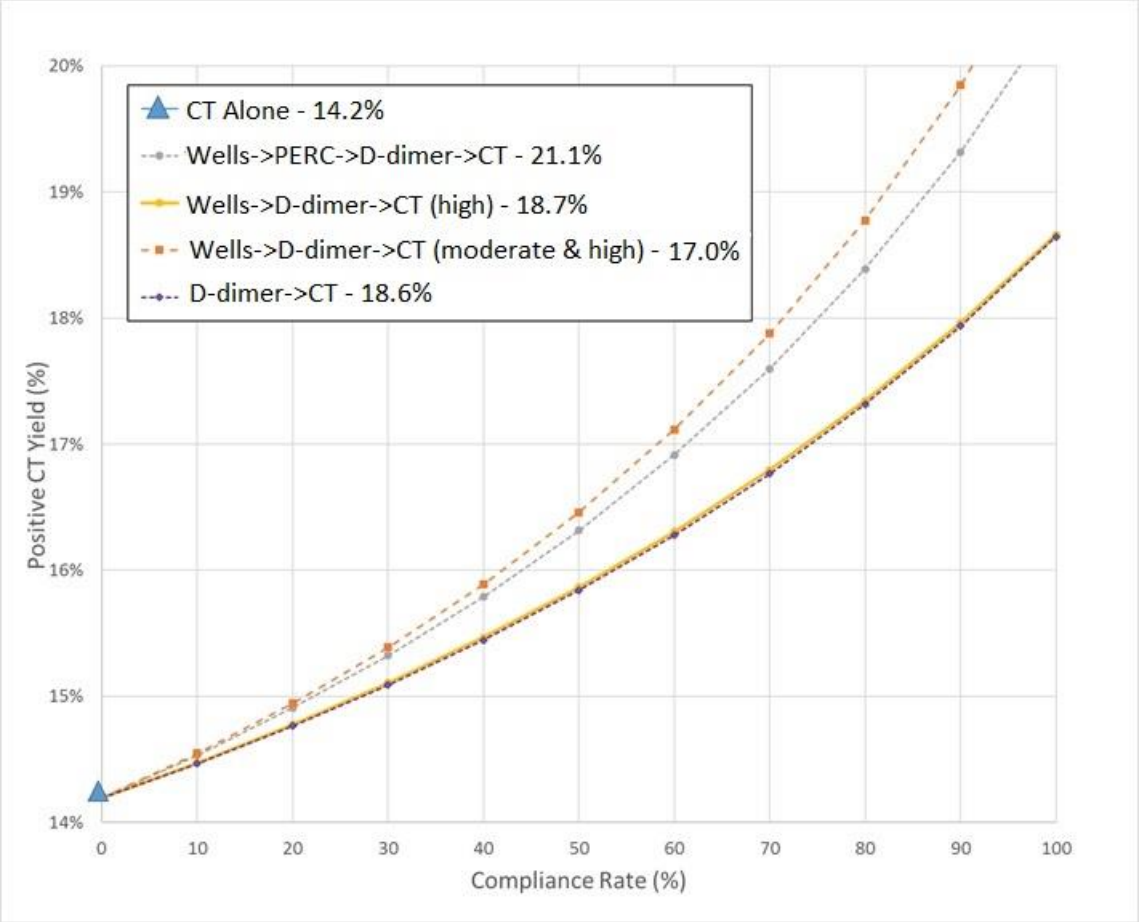
Strategy	Patients with CT (%)	Costs ($)		Percent Diagnosed (%)				Effectiveness (QALYs)			
		Dx Costs	Tx Costs	TP	FP	TN	FN	TP	FP	TN	FN
Wells→PERC→D-dimer→CT	48.3	440.61	1508.09	7.45	2.77	87.98	1.79	0.85	0.35	11.17	0.15
D-dimer→CT	58.7	506.91	1556.46	7.45	3.49	87.26	1.80	0.85	0.44	11.08	0.15
Wells→D-dimer→CT (high)	59.7	526.56	1557.53	7.59	3.56	87.20	1.65	0.86	0.45	11.07	0.14
Wells→D-dimer→CT (moderate and high)	71.6	617.04	1607.53	7.80	4.37	6.38	1.45	0.89	0.55	10.97	0.12
CT alone	100	823.38	1738.75	7.84	6.35	84.40	1.41	0.89	0.81	10.72	0.12

QALY = quality-adjusted life year; PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography; Dx = diagnostic; Tx = treatment; FN= false negative, FP= false positive, TN= true negative, TP= true positive

The percent of patients receiving a CT ranged from 48.3% for the Wells→D-dimer→PERC→CT strategy to 100% for the CT alone strategy (Table 23). Yield ranged from 14.2% (CT alone) to 21.1% with Wells→D-dimer→PERC→CT (Figure 23). Strategies with more risk stratification (Wells', PERC, D-dimer) had higher yield as these strategies remove patients with a low probability of having a PE from being diagnosed by CT. However, strategies with increased yield were also more likely to mis-diagnosis patients that had PE and miss necessary treatment of PE.

Not all interventions that encourage the use of risk stratification tools will have the same compliance. For instance communication interventions were found to have lower yields than guidelines. Furthermore, depending on how demanding a clinical decision support is, i.e. whether ordering a CT requires completion or not, will affect the compliance of its use. Assuming physicians normally use CT alone for diagnosing PE, Figure 23 illustrates the influence of compliance to the various interventions on the diagnostic yield of CT. With greater compliance to each intervention, the greater the improvement in diagnostic yield of CT. For example, with a 50% compliance to Wells→PERC→D-dimer→CT (represented by the gray line) the yield is 16.3%, with 80% compliance this increased the yield to 18.4%.

Figure 23. Yield versus compliance rate of the intervention



PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography

8.4.3 Sensitivity Analysis Results

Results of the sensitivity analyses are presented in Table 24. Overall conclusion of these results were that the model was not sensitive to changes in parameters with respect to: age, proportion of patients male, discount rate, cost of Wells' clinical decision support tool and the time to complete clinical decision rule (Wells' and/or PERC).

When considering a time horizon of only 3 months, QALYs across all strategies were equal (0.195 QALYs) and Wells→PERC→D-dimer→CT was the lowest cost resulting in it being the dominant strategy. With a time horizon of one year, Wells→PERC→D-dimer→CT remains the least costly strategy.

Reducing the prevalence of PE among suspected PE more than doubled the ICUR for Wells→D-dimer→CT (moderate and high) compared to the base case of Wells→PERC→D-dimer→CT ($30,300/QALY gained versus 75,267/QALY gained). Wells→PERC→D-dimer→CT had greater accuracy in identifying patients without PE, thus, a lower prevalence reduced the number of patients diagnosed with PE. When the prevalence of PE among suspected PE was doubled, the ICUR was more than halved for Wells→D-dimer→CT (moderate and high) compared to the base case of Wells→PERC→D-dimer→CT ($30,000/QALY gained versus $13,200/QALY gained).

The model was also sensitive to doubling the risk of CTEPH. In this scenario CT alone was the cost-effective option at an ICUR of $50,000 per QALY. This occurs since CT alone results in the highest probability of identifying a true positive, therefore if the consequences of not treating a true positive were very severe than CT alone was the preferred strategy.

Table 24. Sensitivity Analyses - Sequential ICUR

	Strategy[%] ($/QALY)				
Sensitivity Analysis	**W+P+DD+CT**	**DD+CT**	**W+DD+CT**	**W+DD+CT2**	**CT**
Reference Case	-	Dominated	Dominated	30,300	364,900
Age (55)	-	Dominated	Dominated	21,040	366,400
Male (40%)	-	Dominated	Dominated	Dominated	73,750
Time horizon (3 month)	-	Dominated	Dominated	Dominated	Dominated
Time horizon (1 year)	-	Dominated	Dominated	218,200	Dominated
Discount Rate (5%)	-	Dominated	Dominated	42,760	363,900
Cost of Wells clinical decision support tool (double)	-	Dominated	Dominated	30,186	364,900
Cost of Wells clinical decision support tool (half)	-	Dominated	Dominated	30,371	364,900
Time to complete clinical decision rule of Wells and PERC (0 minutes)	-	Dominated	Dominated	32,814	364,900
Time to complete clinical decision rule of Wells and PERC (10 minutes)	-	Dominated	Dominated	27,800	364,900
Probability of CTEPH (double)	-	Dominated	Dominated	35,350	41,558
Probability of CTEPH (half)	-	Dominated	Dominated	30,314	364,899
Prevalence of PE among suspected PE (double)	-	Dominated	Dominated	13,200	163,600
Prevalence of PE among suspected PE (half)	-	Dominated	Dominated	75,267	383,800

[%]W+P+DD+CT = Wells→PERC→D-dimer→CT; DD+CT = D-dimer→CT; W+DD+CT = Wells→D-dimer→CT (high); W+DD+CT2 = Wells→D-dimer→CT (moderate and high); CT = CT alone
QALY = quality-adjusted life year; ICUR = incremental cost-utility ratio; PERC = Pulmonary Embolism Rule-out Criteria; PE = pulmonary embolism; CTEPH = chronic thromboembolic pulmonary hypertension

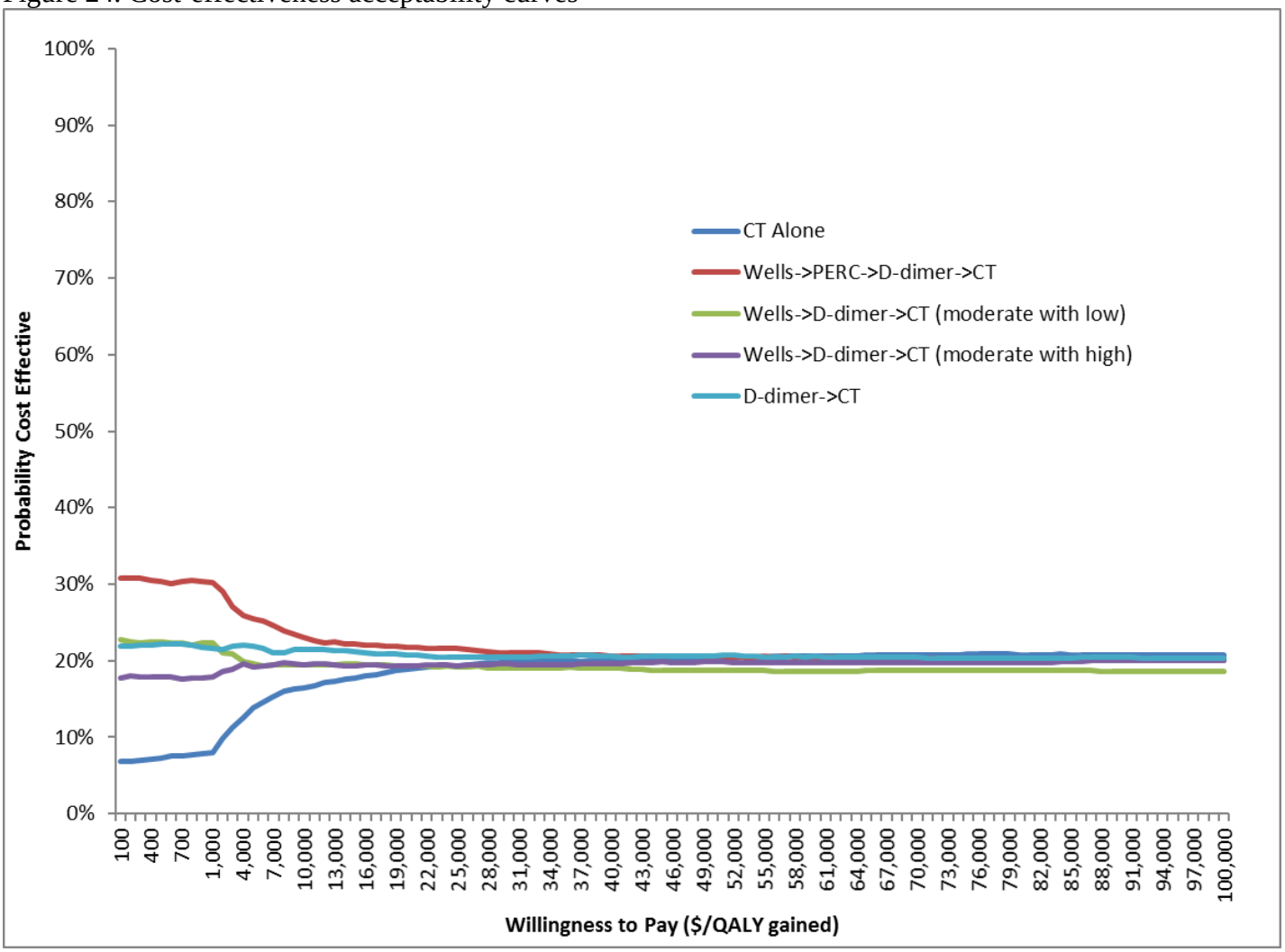
8.4.4 Probabilistic Sensitivity Analysis Results

After 2,500 simulations, Wells→PERC→D-dimer→CT dominated all other strategies except for CT alone. CT alone resulted in an ICUR of $114, 669 per QALY gained compared to Wells→PERC→D-dimer→CT.

Cost-effectiveness acceptability curves for each of the five strategies are presented in Figure 24. When only cost-savings are valued (at a willingness-to-pay (WTP) value of zero for additional QALYs gained), the preferred strategy was Wells→PERC→D-dimer→CT with a probability of being the most cost-effective strategy of 30.7%. Wells→PERC→D-dimer→CT had the highest probability of being the most cost-effective strategy from a WTP value of 0 to approximately $25,000/QALY gained. For WTP values greater than $25,000/QALY gained up to

$100,000/QALY gained, all five strategies have approximately 20% probability of being cost-effective. This was the case as QALYs gained with each strategies were almost equivalent.

Figure 24. Cost-effectiveness acceptability curves



QALY = quality-adjusted life year; PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography

8.4.5 Comparison of results to CADTH's model

In the summer of 2017 CADTH released a draft report "Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism: A Health Technology Assessment". This report considered the costs and benefits of 120 different strategies for diagnosing pulmonary embolism. In addition to the tools considered in our report, CADTH also considered Wells 2 tier, Geneva, Gestalt and Leg Ultra-Sound. The CADTH analysis found that Gestalt->D-dimer->Leg Ultra-Sound->CT scan

was the cost-effective option at a threshold of $50,000 per QALY. This differs from the results of our report that found that Wells->D-dimer->CT was the cost-effective option. Most importantly we did not include Leg Ultra-Sound as an option in our diagnostic strategies because no study looking at interventions for the optimal use of CT included Leg Ultra-Sound nor was it included in the guidelines. Although both our analysis and the CADTH analysis used the same structural model, some of the model inputs differed (Table 25).

Table 25. Important Differences in Model Inputs

Model Input	Our Model	CADTH Model
Prevalence of PE	9.25%	15.2%
Sensitivity of CT	84.8%	97.2%
Specificity of CT	93.0%	98.7%
Sensitivity of Wells	36.9%	13.2%
Specificity of Wells	97.8%	97.2%
Cost of CT	$725	$580

A sensitivity analysis using the above CADTH inputs was run in our model. Overall costs were higher and QALYs were lower using the CADTH inputs due to the higher prevalence of PE (Table 26). However, strategies that use more CT scans resulted in lower costs and higher QALYs using the CADTH model inputs compared to our reference case. This is due to the higher diagnostic accuracy of CT, the lower cost of CT, and the higher prevalence of PE. Overall, this combination of inputs resulted in CT alone being the cost-effective option at $50,000 per QALY with an ICUR of $43,000 per additional QALY.

Table 26. Model Results with CADTH Inputs

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
Wells→PERC→D-dimer→CT	2561	-	12.417	-	-
D-dimer→CT	2609	48	12.425	0.008	6000
Wells→D-dimer→CT (high)	2627	18	12.428	0.003	Extendedly Dominated
Wells→D-dimer→CT (moderate and high)	2695	68	12.443	0.015	4,778
CT alone	2867	172	12.447	0.004	43,000

8.5 Budget Impact Analysis

8.5.1 Budget Impact Analysis Methods

As previously estimated in the cost-effectiveness section, the number of people who are suspected of PE was estimated to be 7,000 individuals. This was the target population for the budget impact analysis. The time horizon for the budget impact analysis was five years, it was assumed a clinical decision support tool's lifetime was five years and that one tool was needed for all of British Columbia; this would be a total cost of $30,000 for the first year of implementation and $5,000 for annual maintenance. Once a clinical decision support tool was in place, there is no limit on the capacity of the tool in the number of people that can be assessed with a Clinical Score. We simulated the total budget impact of each strategy over 5 years assuming an annual cohort of 7000 cases followed for a maximum of 5 years. For example, in the year 1 post-implementation, we assume 7000 cases based on the estimated incidence. In year 2 post-implementation, we have 7000 incident cases associated with year 1 costs and 7000 prevalent cases associated with year 2 costs. We continue this pattern to year 5 post-implementation.

The current scenario in British Columbia was no intervention with a clinical decision support tool and all patients are diagnosed with PE by CT (CT alone strategy). Projected scenarios included implementation of either: Wells→PERC→D-dimer→CT or Wells→D-dimer→CT (moderate and high). Costs and diagnostic accuracy for Wells' Score, PERC, D-dimer testing, and CT were based on values previously utilized in the cost-effectiveness analysis. Similarly, treatment costs from the cost-effectiveness analysis were incorporated for patients who had PE (true positives, false negatives) and those who are incorrectly diagnosed with PE (false positives). However, as patients who were true negative did not receive further treatment, the costs associated with these patients were only those short-term diagnostic costs of the strategy. The total annual costs of each of these outcome groups is presented in Table 27. Costs considered include program costs for the clinical decision support tool (implementation and annual), diagnostic costs (risk stratification by Wells' Score, PERC, D-dimer testing, and CT), and future treatment costs for PE. Costs were based on the number of people presenting to the emergency department suspected of PE.

Table 27. Total annual cost per patient by diagnostic test and disease outcome

Total annual costs by year	TP	FP	FN
Year 1	$6,082	$6,052	$1,483
Year 2	$188	$172	$752
Year 3	$187	$172	$589
Year 4	$21	$1	$432
Year 5	$21	$1	$321

TP = true positive; FP = false positive; FN = false negative, True negatives have a $0 total annual cost

The average cost per Wells score is $10.70, per PERC score is $10.70, per D-Dimer is $23.60 and the average cost per CT is $823. Full details of these costs are provided in Table 18.

8.5.2 Budget Impact Analysis Results

The overall results of the budget impact analysis for implementing a clinical decision support tool (Wells→PERC→D-dimer→CT or Wells→D-dimer→CT (moderate and high)) in British Columbia are presented in

Table 28. The one-year budget impact of the current scenario of CT only was $11.9 million and the incremental budget impact of the clinical decision support tools was a cost avoidance of $4.1 million (Wells→PERC→D-dimer→CT) and $2.2 million (Wells→D-dimer→CT (moderate and high)). The incremental budget impact over a five-year time horizon was estimated at $11.6 to $20.9 million in costs avoided for all of British Columbia for Wells→D-dimer→CT (moderate and high) and Wells→PERC→D-dimer→CT, respectively (Table 29).

Table 28. Budget impact results: 1 year

Costs, $	**Wells→PERC→ D-dimer→CT**	**Wells→D-dimer→ CT (moderate and high)**	**CT alone**
Clinical Decision Support Tool			
Implementation	30,000	30,000	0
Annual Maintenance	5,000	5,000	0
Wells' Score*	74,865	74,865	0
PERC *	47,932	-	0
D-dimer	132,357	105,760	0
CT	2,982,917	4,127,667	5,763,660
Total Diagnostic Costs	3,273,070	4,343,292	5,763,660
Treatment costs			
TP	3,173,257	3,319,481	3,338,724
FP	1,173,131	1,851,072	2,691,223
FN	186,262	150,606	145,917
Total Treatment Costs	4,532,649	5,321,169	6,175,864
Total Budget Year 1	***7,805,720***	***9,664,461***	***11,939.524***
1 year cost difference compared to CT alone	***-4,133,804***	***-2,275,063***	

PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography; TP = true positive; FP = false positive; FN = false negative

*Costs of the physician time

Table 29. Budget impact results: 5 years

Costs, $	**Wells→PERC→ D-dimer→CT**	**Wells→D-dimer→ CT (moderate and high)**	**CT alone**
Clinical Decision Support Tool			
Implementation	30,000	30,000	0
Annual Maintenance	5,000	5,000	0
Wells' Score*	74,865	74,865	0
PERC *	47,932	-	0
D-dimer	132,357	105,760	0
CT	2,982,917	4,127,667	5,763,660
Total Diagnostic Costs	3,273,070	4,343,292	5,763,660
Treatment costs			
Incident cohort	4,532,649	5,321,169	6,175,864
Total Budget Year 1	**7,805,720**	**9,664,461**	**11,939.524**
Clinical Decision Support Tool: Annual Maintenance	5000	5000	0
Treatment costs			
Treatment and diagnostic costs of incident cohort	7,770,720	9,629,461	11,939.524
Treatment of prevalent cohort	225,497	231,158	253,197
Total Budget Year 2	**8,001,217**	**9,865,619**	**12,192,720**
Clinical Decision Support Tool: Annual Maintenance	5000	5000	
Treatment costs			
Treatment and diagnostic costs of incident cohort	7,770,720	9,629,461	11,939.524
Treatment of prevalent cohort	430,577	445,822	490,448
Total Budget Year 3	**8,206,297**	**10,080,282**	**12,429,971**
Clinical Decision Support Tool: Annual Maintenance	5000	5000	
Treatment costs			
Treatment and diagnostic costs of incident cohort	7,770,720	9,629,461	11,939.524
Treatment of prevalent cohort	270,341	501,350	1,035,310
Total Budget Year 4	**8,271,558**	**10,135,811**	**12,484,385**
Clinical Decision Support Tool: Annual Maintenance	5000	5000	
Treatment costs			
Treatment and diagnostic costs of incident cohort	7,770,720	9,629,461	11,939.524
Treatment of prevalent cohort	324,313	547,787	1,080,921
Total Budget Year 5	**8,325,530**	**10,182,247**	**12,529,996**
Total 5 year costs	***40,610,323***	***49,928,420***	***61,576,596***
5 year cost difference compared to CT alone	***-20,966,273***	***-11,648,176***	

PERC = Pulmonary Embolism Rule-out Criteria; CT = computed tomography; TP = true positive; FP = false positive; FN = false negative

*Costs of the physician time

8.6 Discussion

Overall, the economic model estimated very small differences in health benefits (QALYs gained) between interventions for diagnosing PE in British Columbia. Total QALYs gained per intervention ranged from 12.489 with Wells→PERC→D-dimer→CT to 12.497 with CT alone, suggesting the largest incremental difference of 0.001 QALYs (or 0.4 quality-adjusted life days) gained in favour of CT alone. Results were robust to most sensitivity analyses undertaken. However, the results were sensitive to prevalence of PE among suspected PE, time horizon and the risk of CTEPH. Total costs per intervention ranged from $1981 with Wells→PERC→D-dimer→CT to $2558 with CT alone, suggesting costs avoided of $577 with Wells→PERC→D-dimer→CT compared with CT alone. The deterministic results were slightly different than the probabilistic results. The deterministic results suggest that Wells→D-dimer→CT (moderate and high) may be a cost-effective option, where the probabilistic analysis suggests this strategy is dominated by Wells→PERC→D-dimer→CT. With respect to yield, interventions improved the positive yield of CT by 2.8 to 6.9% compared to CT alone (yield of 14.2%). When considering only costs avoided, Wells→PERC→D-dimer→CT had the highest probability of being cost-effective compared to all other interventions (30.9%). However, as the WTP value increased and health benefits are valued greater, all five interventions had approximately 20% probability of being cost-effective. This is likely due to the very similar QALYs gained with each intervention. The budget impact analysis suggested that instituting a decision support tool (Wells→PERC→D-dimer→CT or Wells→D-dimer→CT (moderate and high) would save $2.2 to 4.1 Million in the first year. Over five years, $11.6 to 20.9 million in costs avoided for all of British Columbia for Wells→D-dimer→CT (moderate and high) and Wells→PERC→D-dimer→CT, respectively.

8.6.1 Limitations

There are some limitations with the economic model. Informal care costs were not taken into account in the model and some of the costs were from other provinces (mostly Ontario). Costs to the physician associated with potential legal suits for missing a diagnosis were not included, although legal concerns are likely to influence use towards more CT examinations. With respect to the diagnostic accuracy of D-dimer and PERC, the correlation between sensitivity and specificity values were not preserved in the conduct of the probabilistic sensitivity analysis. Although the risk of inappropriate anticoagulation treatment for patients who are incorrectly

diagnosed with PE was explored, other risks such as risk of radiation or contrast reaction associated with CT was not explored. Evidence suggests that 1-3% of the population will have a contrast reaction.[193,194] This suggests that the difference in QALYs of DST strategies compared to the CT alone strategy may be lower.

8.7 Conclusion

A cost-effectiveness analysis and budget impact analysis of interventions incorporating clinical decision support tools (risk stratification by Wells' Score, PERC, and/or D-dimer testing followed by diagnostic imaging with CT) compared with CT alone in diagnosing PE was conducted from the British Columbia public perspective. Results suggest that all interventions, particularly, Wells→PERC→D-dimer→CT, were less costly than CT alone; however, it was also marginally less effective over a lifetime horizon (0.001 QALYs or 0.0016 LY). The budget impact analysis estimated that the implementation of a clinical decision support tool in British Columbia would result in costs avoided over a one- and five-year time horizon, with greatest costs avoided with implementing Wells→PERC→D-dimer→CT.

9 Overall Conclusions

Overall, CT has high sensitivity and specificity for diagnosing PE, with sensitivity ranging from 81.7% to 87.5% and specificity ranging from 90.9% to 94.6%. A pooled stratified meta-analysis suggests that the only intervention type that was significantly effective for increasing CT yield was clinical decision support tools. Barriers such as time pressures and patient demands, as well as facilitators such as staff acceptance and buy-in, may change the success of the intervention and should be considered. Physicians interviewed were unaware of decision support tools for diagnosing PE that would help increase appropriate use of CT, but felt that such a tool would be helpful. Results from the cost-utility model suggest that an intervention of Wells→PERC→D-dimer→CT had the lowest costs with a total of $1981 and effectiveness of 12.489 QALYs. Wells→D-dimer→CT resulted in an ICUR of $30,000 per QALY gained compared to the baseline strategy of Wells→PERC→D-dimer→CT. CT alone had the highest ICUR, of $364,900 per QALY gained compared to Wells→D-dimer→CT. CT alone resulted in the highest total QALYs, as CT is more accurate at diagnosing PE than interventions with risk stratification. However, it is only marginally better than Wells→D-dimer→CT (moderate and high) with an

incremental QALY gain of 0.001 (0.4 quality-adjusted life days) over a lifetime time horizon. The budget impact analysis suggests that instituting a decision support tool with Wells→PERC→D-dimer→CT may result in substantial cost avoidance for the healthcare system.

10 References

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Appendix A: Diagnostic Accuracy

Table A1: Clinical Effectiveness Database Search Strategy

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
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/
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/
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/
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.
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

Table A2: Detailed Characteristics of Included Studies

Author, Year, Country	Study Characteristics	Participant Details	Intervention	Reference standard	Outcomes Measured	Quality
Lu, 2014 China	*Study Design:* RCT *Period of Data Collection:* May 2013 – December 2013 *Setting of conduct:* single center. Imaging unit of a hospital.	*Number of included participants:* 100 *Inclusion Criteria:* patients who were referred to the imaging department for a clinically indicated CTPA for suspected PE were included in this study. *Exclusion Criteria:* patients with a history of allergy to iodinated contrast agent, age less than 18 years, pregnant women, hyperthyroidism and body weigh exceeding 80 kg. *Participant demographics*: Group A and B - 52.4±16.2 vs. 54.5±15.8 years. Group A and B – 29 vs 27 male	*Type*: Dual source CT *Details*: CTPA - group A, 100 kVp, 1.2 pitch, 60 ml of contrast medium and filtered back projection algorithm; CTPA - group B, 80 kVp, 2.2 pitch, 20 ml of contrast medium and sinogram affirmed iterative reconstruction	*Type*: Consensus reading *Details*: un-blinded consensus reading of readers was regarded as the reference standard	Image quality, diagnostic accuracy and radiation dose	At risk of bias
Megyeri, 2014 Switzerland	*Study Design:* Retrospective NRS *Period of Data Collection:* September 2007 – April 2011 *Setting of conduct:* single center. Emergency care unit of a tertiary-care center	*Number of included participants: 123 (Body Weight > 100kg); 114 (Body Weight < 100 kg)* *Inclusion Criteria:* patients weighing ≥100 kg who underwent CTPA to exclude PE	Type: Multi detector CT Details: 16-row CT scanner by using 16 × 0.75 mm collimation,	Type: Composite reference standard Details: clinical probability, reference CTPA result, additional imaging when	Diagnostic accuracy of CTPA in two patient groups	At risk of bias

		The control group consisted of 114 patients weighing 75 to 99 kg who underwent CTPA. *Exclusion Criteria:* Not reported *Participant demographics*: Age - BW > 100kg: 57.8 +/- 14.8 years. BW < 100kg: 59.2 +/- 15.8 years. <100 kg group (n=114; 81=M, 33=F); >=100 kg group (n=123; 94=M, 29=F)	1.15 pitch, tube voltage was set at 100 kVp and the quality reference tube current time product at 100 mAs.	performed, and 90-day follow-up		
Okada, 2015 Japan	*Study Design:* Retrospective NRS *Period of Data Collection:* April 2012 – March 2013 *Setting of conduct:* single center. Setting unclear.	*Number of included participants:* 83 *Inclusion Criteria:* Included all initial weighted average CTPA using the dual-energy technique performed *Exclusion Criteria*: presence of motion artifact caused by insufficient breath-holding or previous history of PE *Participant demographics*: Age - 64.5 +/- 15.1 years 31 males and 50 females	Type: Multi detector CT Details: 64-slice dual-source CT, detector collimation was set to 64mm×0.6mm, the gantry rotation time was 0.33s, and the pitch value was 0.5, CTPA using dual-energy technique was started with bolus tracking	Type: Combined tests Details: CTPA / LPBV + clinical and physical findings	Number and locations of intra-pulmonary clots, Diagnostic accuracy values	At risk of bias

			measurement in the pulmonary artery at a threshold of 100HU			
Stein, 2006 International	*Study Design:* Prospective NRS *Period of Data Collection:* September 2001 – July 2003 *Setting of conduct:* Multi center. Inpatient or outpatient clinical centers	*Number of included participants:* 773 *Inclusion Criteria:* Patients who were at least 18 years of age and had clinically suspected acute pulmonary embolism. Patients who were referred for diagnostic imaging for suspected pulmonary embolism. Patients for whom the study nurse was aware of a consultation request for suspected pulmonary embolism. *Exclusion Criteria: unable to complete testing within 36 hr; abnormal creatinine levels or were receiving long-term renal dialysis; history of long-term anticoagulant use; critically ill receiving ventilatory support; allergic to contrast agents; myocardial infarction within preceding month; possible pregnancy;* *inferior vena caval filter in situ; no suspected pulmonary embolism; upper-extremity DVT; previously enrolled in the study; VF or sustained VT within 24 hr; shock or hypotension; Planned to have thrombolytic therapy within the next*	Type: Multi detector CT Details: 4-row, 8-row, or 16-row multi-detector scanners. For patients <250 pounds scanned on 4-slice equipment, collimation was 1.25 mm, table speed 7.5 mm/rotation, pitch 1.5 (usually between 1.0-2.0), voltage 120 kVp, current 400 mA, and rotation time approximately 0.8 seconds.	Type: Composite reference standard Details:	Diagnostic accuracy of CT	At risk of bias

		24 hr; less than 18 years of age; *Participant demographics*: Age - 51.7 +/- 17.1 years 62% females				
Coche, 2003 Belgium	*Study Design:* Prospective NRS *Period of Data Collection:* 21 months *Setting of conduct:* single center. Emergency department of urban teaching hospital with an annual census of 50,000 patients	*Number of included participants:* 94 *Inclusion Criteria:* clinical suspicion of PE, age greater than 18 years, absence of clinically suspected deep venous thrombosis, and plasma D-dimer levels greater than 500 ng/mL *Exclusion Criteria:* D-dimer test that was negative; clinical signs of deep venous thrombosis; D-dimer values that were positive with an obvious alternative diagnosis; incomplete study protocols; contraindications to spiral CT; patient transfer; death; and patient refusal or inability to participate. *Participant demographics*: Age - 62 ± 18 years 66 [70%] were female and 28 male	Type: Multi detector spiral CT Details: thin-collimation multi– detector row CT (collimation, 4 x 1 mm; pitch, 1.25, 120 kV, and 144 mAs.)	Type: Combined tests Details: Ventilation-perfusion (V-P) scintigraphy, pulmonary digital subtraction angiography when indicated, and chest radiography	Episodes of recurrent or new deep venous thrombosis or PE; Diagnostic accuracy of CT	At risk of bias
Quandli, 2000 France	*Study Design:* Prospective NRS *Period of Data Collection:* September 1996 – August 1998 *Setting of conduct:* single center.	*Number of included participants:* 158 *Inclusion Criteria:* age of 18–75 years, a clinical suspicion of acute PE (dyspnea, chest pain, hemoptysis, syncope, risk factors for	Type: Dual section helical CT Details: Pulmonary	Type: Pulmonary Arteriography Details: Pulmonary digital subtraction arteriography was	Presence of PE, CT Sensitivity, CT Specificity	At risk of bias

	Department of radiology	thromboembolic disease, abnormal findings at chest radiography or electrocardiography, or abnormal arterial blood gas test results), and the mental ability to give informed consent. *Exclusion Criteria: having clinical signs of life-threatening PE (seven had cardiogenic shock or acute right ventricular failure), renal failure (six had a creatinine clearance level of less than 35 mL per minute by using the Cockroft formula or had previously used nephrotoxic drugs), or a history of allergy to iodinated contrast media (five patients). Twenty-six patients refused CT. Two patients were excluded after selective arteriography* *Participant demographics*: Age Range 23 - 75 years 73 Males / 85 Females	dual-section helical CT was performed by using 120 kV; 199 mA; 5-mm collimation (2 x 2.5 mm); 7.5 mm/sec table speed (pitch, 1.5); 15-cm z-axis coverage; and a 20-second scanning time.	performed in all patients by using a transfemoral venous approach and the Seldinger technique.		
Wang, 2009 China	*Study Design:* Prospective NRS *Period of Data Collection:* November 2000 – May 2001 *Setting of conduct:* single center. Department of internal medicine	*Number of included participants:* 82 *Inclusion Criteria:* Included patients with normal creatinine level and were willing to undergo VQ scan and CTPA. *Exclusion Criteria:* Pregnant women, patients who were currently	Type: Multi detector CT Details: CT Images were obtained with a 16 or 64-detector CT scanner after	Type: Composite reference standard Details: based upon all imaging modalities, all available laboratory recorders, clinical	Diagnostic accuracy values	At risk of bias

		experiencing circulatory shock or had hypotension or renal failure, were hemodynamically unstable, were on ventilatory support, had chronic pulmonary hypertension, received anticoagulation, or had a history of allergy to contrast media. *Participant demographics*: Age Range 14 – 81 years 41 men / 41 women	intravenous injection of contrast medium. Interpretation was based on effective axial slice thickness of 1.25 mm. Scans were performed from the level of the aortic arch to 2 cm above the diaphragm.	data, the opinions of the physicians responsible for treatment and outcomes.		
Winer-Muram, 2004 USA	*Study Design:* Prospective NRS *Period of Data Collection:* September 1999 - March 2001 *Setting of conduct:* single center. emergency room and inpatient populations of tertiary care center and a public hospital	*Number of included participants:* 93 *Inclusion Criteria:* Patients who were suspected of having acute PE on the basis of clinical presentation were eligible for the study. *Exclusion Criteria:* age of less than 18 years, serum creatinine levels of more than 1.5 mg/dL (132.6 mol/L) within the previous 24 hours (unless the patient was undergoing hemodialysis for chronic renal failure), history of severe allergic reaction to iodinated contrast material, pregnancy or possibility of pregnancy, and recent lower-extremity US study that demonstrated deep venous thrombosis.	Type: Multi detector CT Details: CT examinations were performed by using a four-channel multi–detector row CT scanner. Scanning was performed using 10-mm nominal collimation (4 x 2.5 mm), with an effective section width of 3.2 mm, a	Type: Pulmonary Arteriography Details: All studies were performed with either a DFP-2000A angiographic unit or an Integris V3000 angiographic unit.	Presence of PE, CT Sensitivity, CT Specificity	At risk of bias

		Participant demographics: Age Range: 19 - 88 years 39% males / 61% females	gantry rotation speed of 0.5 seconds, a table speed of 20 mm/sec, a pitch of 1, a tube voltage of 120 kV, and a tube current of 200–300 mAs.			
Blachere, 2000 France	*Study Design:* Prospective NRS *Period of Data Collection:* 18 months *Setting of conduct:* single center. inpatients, outpatient, intensive care unit	*Number of included participants:* 179 *Inclusion Criteria:* clinically suspected of having acute pulmonary embolism *Exclusion Criteria: any contraindication for the use of iodine contrast material (renal failure, history of allergy), unstable hemodynamic status, and pregnancy.* *Participant demographics*: mean age of 61 years (range, 20–88 years) 88 men and 91 women	Type: Helical CT Details: Technical parameters included 3-mm (n =82) or 2-mm (n = 134) collimation, 1.8–2.0 pitch, 120 kV, 170 mA, and 0.75-sec scan time. The choice of collimation was made according to the patient's capacity to breath-hold.	Type: Combined tests Details: All patients underwent ventilation–perfusion radionuclide lung scanning, contrast-enhanced helical CT angiography, and Doppler sonography of the legs	recurrence of PE or of a VTE Diagnostic accuracy of CT	At risk of bias
Ohno, 2004 USA	*Study Design:* Prospective NRS *Period of Data Collection:* Not reported	*Number of included participants:* 48 *Inclusion Criteria:* Clinically suspected PE	Type: Multi detector CT Details: The	Type: pulmonary angiography Details:	Diagnostic accuracy of CT	At risk of bias

	Setting of conduct: single center. Setting unclear	*Exclusion Criteria:* Not reported *Participant demographics*: Mean age 55 years (range 27-73) Male 26; Female 22	scans were obtained with 140 kVp; 110 effective mAs; collimation, 4 x 1 mm; pitch, 6:1; reconstruction collimation, 1.25 mm; and scanning rotations, 500 msec. During scanning, 100 mL of contrast material was administered to patients IV via an antecubital vein at 4 mL/sec with a power injector with an empiric scanning delay of 20 sec.			
Reinartz, 2004 Germany	*Study Design:* Retrospective NRS *Period of Data Collection:* January 2001 to April 2003 *Setting of conduct:* single center. Setting not reported.	*Number of included participants:* 83 *Inclusion Criteria:* patients who had V/Q lung scintigraphy in SPECT technique as well as multi-slice spiral CT within an interval of 3 days *Exclusion Criteria:* Not reported	Type: Multi slice spiral CT Details: MSCT examinations of the chest were done using a 4-detector row scanner after	Type: Consensus reading Details: The final diagnosis was made at a consensus meeting while taking into account all imaging modalities,	Diagnostic accuracy data	At risk of bias

		Participant demographics: mean age (SD) - 53.9 +/- 19.5 years (range 18-88) Male 36; Female 47	intravenous application of 120 mL contrast medium at a flow rate of 3 mL/s. Scan parameters were 120 kV and 100 mA, using a thin collimation of 4 _ 1 mm and a table speed of 7 mm per rotation. Tube rotation time was 0.5 s.	clinical data, D-dimer levels, the opinions of the physicians responsible for treatment, and a clinical follow-up of at least 5 months		
Reissig, 2001 Germany	*Study Design:* Prospective NRS *Period of Data Collection: February 1998 to March 2000* *Setting of conduct:* single center. Setting not reported.	*Number of included participants:* 69 *Inclusion Criteria:* Not reported *Exclusion Criteria:* Not reported *Participant demographics*: mean age 62.8 years (range 24-88) Male 42; Female 27	Type: Spiral CT Details: No details reported	Type: Combined tests Details: CTPA and transthoracic sonography	Diagnostic accuracy data	At risk of bias
He, 2012 China	*Study Design:* NRS. Cross sectional *Period of Data Collection:* June 2007 to January 2011 *Setting of conduct:* Multi center. Secondary care centers (including academic centers).	*Number of included participants:* 544 *Inclusion Criteria:* Patients with suspected PE (based on signs and symptoms, laboratory findings, medical history and predisposing factors - assessed formally by Wells) *Exclusion Criteria: Abnormal serum creatinine; unwilling to uncergo V/Q; chest X-ray, and CTPA; pregnancy; circulatory shock; hypotension; renal*	Type: Multi detector CT Details: Scan parameters for CT: Injection to scan delay of 14s; 120 kV and 300 mA using thin collimation of 64 x 0.625 mm	Type: Composite reference standard Details: clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g., echocardiography), CTPA, V/Q, right heart cardiac	Diagnostic accuracy data	At risk of bias

		failure; hemodynamically unstable; ventilatory support; anticoagulation; history of allergy to contrast media; received thrombolytic therapy before examinations excluded *Participant demographics*: mean age (SD) - 53.3 +/- 16.9; Range = 20 to 91 235 Men (43.2%) /309 Women (56.8%)	(supine, breath-hold). 75 to 85 mL contrast medium at 5 mL/s with double power injector.	catheterization, and PA (performed in patients with indeterminate tests by other modalities) as well as physician opinions and 6-month clinical follow-up		
Nilsson, 2002 Sweden	*Study Design:* Prospective NRS *Period of Data Collection:* March 1999 and May 2001 *Setting of conduct:* Single center. Emergency ward.	*Number of included participants:* 90 *Inclusion Criteria:* Hemodynamically stable outpatients with symptoms of acute PE presenting during the daytime *Exclusion Criteria: Pregnancy, previous adverse reactions to contrast media, renal insufficiency (serum-creatinin >150 mmol/l), treatment with metformine, ongoing anticoagulation therapy, two or more previous VTE events, severe malnutrition or cachexia, expected survival less than 3 months, advanced psychiatric disorder, thrombocytopenia (TPK <70 X 109/l), known hepatitis or HIV infection, acute myocardial infarction or unstable hemodynamics.*	Type: Spiral CT Details: Scan parameters are 3 mm collimation and a table speed of 3 to 5 mm/s (pitch of 1.3 to 1.7). The tube current was 200 to 210 mA, the rotation time 0.8 to 1 second, and the tube voltage 120 kV.	Type: Pulmonary Angiography Details: PA examinations used Siemens High Cor or Philips Integris digital, single plane angiographic equipment at 12.5 or 25 frames per second. PA was performed with the standard Seldinger technique using the femoral approach. At least two oblique projections of each lung were performed.	Diagnostic accuracy data	At risk of bias

		Participant demographics: Mean age 49.5 ± 15 years 47% males / 53% females				

Table A3: Quality assessment of included studies as assessed by the QUADAS-II

QUADAS Assessment Item	**Megyeri[117]**	**Okada[116]**	**Stein[120]**	**Coche[118]**	**Qanadli[112]**	**Wang[108]**	**Winer-Muram[110]**	**Blachere[113]**	**Ohno[111]**	**Reinartz[114]**	**Reissig[115]**	**He[109]**	**Nilsson[119]**
Was a consecutive or random sample of patients enrolled?	Low	Unclear	Low	High	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Low
Was a case-control design avoided?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Did the study avoid inappropriate exclusions?	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low
Are there concerns that the included patients and setting do not match the review question?	Unclear	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	High	Low	Low
Were the index test results interpreted without knowledge of the results	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Unclear	Low

of the reference standard?													
If a threshold was used, was it prespecified ?	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear	Low	Low
Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Low	Low
Is the reference standard likely to correctly classify the target condition?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Were the reference standard results interpreted without knowledge of the results of the index test?	High	Low	Low	Unclear	Low	High	Low	Low	Unclear	Unclear	Low	High	Low
Are there concerns that the target condition as defined by the reference standard	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Low	Low	Low

does not match the question?													
Was there an appropriate interval between the index test and reference standard?	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	Low
Did all patients receive the same reference standard?	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Unclear	Low
Were all patients included in the analysis	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low

Appendix B: Patient Perspective

CT and PE Patient Perspective Search

MEDLINE

1. exp Tomography, X-Ray Computed/
2. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
3. (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).tw,kw.
4. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
5. 1 or 2 or 3 or 4
6. exp Pulmonary Embolism/
7. (pulmonary arter* adj5 embolism*).tw,kw.
8. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
9. 6 or 7 or 8
10. patient acceptance of health care/ or patient satisfaction/ or patient preference/
11. health behavior/ or patient compliance/ or treatment refusal/
12. (attitudes or behavior* or behaviour* or experiences or perceptions or preference* or "quality of life" or satisfaction).tw.
13. 10 or 11 or 12
14. 5 and 9 and 13

Embase

1. patient acceptance of health care/ or patient satisfaction/ or patient preference/
2. health behavior/ or patient compliance/ or treatment refusal/
3. (attitudes or behavior* or behaviour* or experiences or perceptions or preference* or "quality of life" or satisfaction).tw.
4. 1 or 2 or 3
5. exp Tomography, X-Ray Computed/
6. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
7. (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).tw,kw.
8. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
9. 6 or 7 or 8
10. exp Pulmonary Embolism/
11. (pulmonary arter* adj5 embolism*).tw,kw.
12. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
13. 10 or 11 or 12

14. 4 and 9 and 13

All EMB Reviews

1. patient acceptance of health care/ or patient satisfaction/ or patient preference/
2. health behavior/ or patient compliance/ or treatment refusal/
3. (attitudes or behavior* or behaviour* or experiences or perceptions or preference* or "quality of life" or satisfaction).tw.
4. 1 or 2 or 3
5. exp Tomography, X-Ray Computed/
6. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
7. (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).tw,kw.
8. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
9. 6 or 7 or 8
10. exp Pulmonary Embolism/
11. (pulmonary arter* adj5 embolism*).tw,kw.
12. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
13. 10 or 11 or 12
14. 4 and 9 and 13

PsychInfo

1. patient acceptance of health care/ or patient satisfaction/ or patient preference/
2. health behavior/ or patient compliance/ or treatment refusal/
3. (attitudes or behavior* or behaviour* or experiences or perceptions or preference* or "quality of life" or satisfaction).tw.
4. 1 or 2 or 3
5. exp Tomography, X-Ray Computed/
6. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
7. (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).tw,kw.
8. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
9. 6 or 7 or 8
10. exp Pulmonary Embolism/
11. (pulmonary arter* adj5 embolism*).tw,kw.
12. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
13. 10 or 11 or 12
14. 4 and 9 and 13

Appendix C: Appropriate Use of CT

Search Strategy

Econlit

15. exp Tomography, X-Ray Computed/
16. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
17. (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).tw,kw.
18. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
19. 1 or 2 or 3 or 4
20. exp Health Services Misuse/
21. (appropriate* or curtail* or cut* back* or cutback* or decreas* or limit* or minimi* or misuse or misusing or moderat* or optimi* or overuse* or reduc* or restrict* or scale back or scaling back or scale down or scaling down).tw,kw.
22. 6 or 7
23. 5 and 8
24. exp Pulmonary Embolism/
25. (pulmonary arter* adj5 embolism*).tw,kw.
26. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
27. 10 or 11 or 12
28. 9 and 13

NHSEED

1. exp Tomography, X-Ray Computed/
2. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
3. (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).tw,kw.
4. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
5. 1 or 2 or 3 or 4
6. exp Health Services Misuse/
7. (appropriate* or curtail* or cut* back* or cutback* or decreas* or limit* or minimi* or misuse or misusing or moderat* or optimi* or overuse* or reduc* or restrict* or scale back or scaling back or scale down or scaling down).tw,kw.
8. 6 or 7
9. 5 and 8
10. exp Pulmonary Embolism/
11. (pulmonary arter* adj5 embolism*).tw,kw.
12. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
13. 10 or 11 or 12
14. 9 and 13

Medline

1. exp Tomography, X-Ray Computed/
2. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
3. (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).tw,kw.
4. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
5. 1 or 2 or 3 or 4
6. exp Health Services Misuse/
7. (appropriate* or curtail* or cut* back* or cutback* or decreas* or limit* or minimi* or misuse or misusing or moderat* or optimi* or overuse* or reduc* or restrict* or scale back or scaling back or scale down or scaling down).tw,kw.
8. 6 or 7

9. 5 and 8
10. exp Pulmonary Embolism/
11. (pulmonary arter* adj5 embolism*).tw,kw.
12. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
13. 10 or 11 or 12
14. 9 and 13
15. limit 14 to (english or french)
16. limit 14 to (comment or editorial or letter)
17. 15 not 16

EMBASE

1. exp Tomography, X-Ray Computed/
2. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
3. (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).tw,kw.
4. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
5. 1 or 2 or 3 or 4
6. (appropriate* or curtail* or cut* back* or cutback* or decreas* or limit* or minimi* or misuse or misusing or moderat* or optimi* or overuse* or reduc* or restrict* or scale back or scaling back or scale down or scaling down).tw,kw.
7. 5 and 6
8. lung embolism/
9. (pulmonary arter* adj5 embolism*).tw,kw.
10. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
11. 8 or 9 or 10
12. 7 and 11
13. limit 12 to (english or french)
14. limit 12 to (conference abstract or conference proceeding or editorial or letter)
15. 13 not 14

Cochrane

1. exp Tomography, X-Ray Computed/
2. ((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).tw,kw.
3. (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).tw,kw.
4.
5. (CTPA or CT pulmonary angiography or CT angiography).tw,kw.
6. 1 or 2 or 3 or 4
7. (appropriate* or curtail* or cut* back* or cutback* or decreas* or limit* or minimi* or misuse or misusing or moderat* or optimi* or overuse* or reduc* or restrict* or scale back or scaling back or scale down or scaling down).tw,kw.
8. 5 and 6
9. lung embolism/
10. (pulmonary arter* adj5 embolism*).tw,kw.
11. ((pulmonary or lung*) adj5 (embol* or microembol* or thromboembol*)).tw,kw.
12. 8 or 9 or 10
13. 7 and 11
14. limit 12 to (english or french)
15. limit 12 to (conference abstract or conference proceeding or editorial or letter)
16. 13 not 14

Table C1: Characteristics

Author, Year, Country	Objective and method	Clinical context	Participant Details	Details of Intervention	Clinical Pathway
Agarwal, 2012, Australia	*Objective:* To investigate the level of adherence to local diagnostic imaging guidelines for suspected PE and to ascertain the impact of interventions *Study Design:* Pre- post-intervention *Methods:* Retrospective audit using Emergency Department Information System and Radiology Information System between September 2005 and March 2006, followed by intervention and prospective post-intervention data collection between January 2008 and March 2008.	Emergency Department in 855 bed public teaching hospital	*Inclusion Criteria:* consecutive patients referred by emergency department of Royal Perth Hospital for CTPA or VQ scan. *Exclusion Criteria:* Patients less than 18 years old, pregnant, d-dimer or imaging requested for diagnosis other than PE *Participant demographics*: **Pre-intervention:** 187 participants, 103 females and 84 males, mean age 55±18 years, 89 underwent CTPA, 98 had VQ **Post-intervention:** 109 subjects, 58 females and 51 males, mean age 59±20 years, 76 underwent CTPA, and 33 VQ.	Diagnostic Imaging Pathways (DIP) online clinical decisions support tool. Intervention included a 1-day teaching session to DIP guidelines, regular reminders at daily handovers *Follow-up Time:* 3 months	Guidelines on the Diagnostic Imaging Pathways considered gold standard which includes the use of Wells score as a primary screening tool to stratify patients into low, intermediate or high risk of PE
Booker, 2016, United States	*Objective:* To optimize the utilization of CT pulmonary angiogram for the diagnosis and workup of acute chest pain to reduce unnecessary radiation and health system expense *Study Design:* Pre- Post-intervention	Emergency department in 700 bed acute care hospital	*Inclusion Criteria:* All patients undergoing CTPA in Scipps Mercy Hospital Emergency Department *Exclusion Criteria:* None reported *Participant demographics*: **Pre-intervention:** 206 patients,	Presentation at monthly emergency department meeting highlighting published protocols and workup for pulmonary embolism including utility of Wells, simplified Wells and PERC scores, overview of D-dimer and CTPA	None reported

	Methods: Retrospective chart evaluation for pulmonary embolism scoring criteria and D-dimer utilization collected from August 2014 to October 2014 followed by intervention starting January 28, 2015 and prospective post-intervention data collection between February 2015 and April 2015.		mean age of 56.2 years, 40.3% male and 59.7% female **Post-intervention:** 206 patients, mean age of 56.7 years, 45,1% male and 54.9% female	utilization within the emergency department. Individual utilization data was sent confidentially to each clinician *Follow-up Time:* 3 months	
Dunne, 2015, United States	*Objective:* To determine the effect of clinical decision support on use and yield of inpatient CT pulmonary angiographic imaging for acute Pulmonary Embolism. *Study Design:* Pre- Post-intervention *Methods:* Retrospective audit prior to intervention implementation on November 1, 2009, and prospective data collection after.	793-bed urban teaching hospital with over 50,000 annual admissions	*Inclusion Criteria:* Patients older than 16 years *Exclusion Criteria:* Patients in hospice care *Participant demographics*: **Pre-intervention:** 3037 CT pulmonary examinations, mean age 57.8 (95%CI: 57.1-58.4), and 40.7% male **Post-intervention:** 2825 CT pulmonary examinations, mean age 57.9 (95% CI 57.3-58.5), and 40.3% male	Clinical decision tool informed providers of the patient-specific pre-test probability for PE based on validated decision rule when they submitted an order for CT. Advice could be accepted and order cancelled, or advice could be ignored. *Follow-up Time:* Not reported	Physician selected clinical suspicion of PE (low, intermediate or high), and D-dimer level to get clinical decision tool support advice
Geetings, 2016, United States	*Objective:* To determine the impact of embedding a pre-test probability rule that is required during the computerized physician order-entry process on the appropriateness of CT angiography of the pulmonary arteries for the diagnosis of pulmonary embolism in the emergency department *Study Design:* Pre- post intervention *Methods:* Data was collected	Emergency department of a tertiary care university hospital, with 62,000 admissions in year 1 of study and 66,000 patients in year 2	*Inclusion Criteria:* All pulmonary CTA examinations ordered for suspected pulmonary embolism *Exclusion Criteria:* Younger than 18 years old *Participant demographics*: **Pre-intervention:** 46,834 patients, mean age 47.9 (SD 20.6), 44.7% male **Post-intervention:** 49,673 patients, mean age 47.6 (SD 20.2), 44% male	Embedding a field for modified Wells score in the CTA order set. Modified wells score was required to order CT, but CT could be ordered regardless of score. *Follow-up Time:* 12 months	Not Applicable

	before the intervention from October 17, 2010 to October 17, 2011. Intervention implemented on October 17, 2011 and post-intervention data was recorded until October 17, 2012				
Hardin, 2008, United States	*Objective:* To evaluate the effectiveness of e-mail communication to reduce the utilization of CT for pulmonary embolism in young patients (age 40 and under) *Study Design:* pre- post-intervention *Methods:* Data were retrospectively collected 90 days prior to email correspondence and retrospectively collected 90 days after email correspondence	Emergency department, details not reported	*Inclusion Criteria:* CT studies in emergency department patients aged 40 and younger *Exclusion Criteria:* None reported *Participant demographics*: **Pre-intervention:** 33 patients, mean age 30.3, age range 19-40, 25 females and 8 males **Post-intervention:** 32 patients, mean age 30.2 years, age range 17-40, 26 females and 6 males.	Email sent to all Emergency Department physicians. Email reported that use of CT to diagnose PE was increasing. To prevent radiation exposure in young females, V/Q scan should be considered as an alternative method of diagnosis. *Follow-up Time:* 1.5 months	V/Q to replace CT scans in patients under 40 years old
Jimenez, 2015, Spain	*Objective:* To determine the effect of an evidence-based clinical decision support algorithm on the use and yield of CT pulmonary angiography and outcomes of patients evaluated in the emergency department for suspected pulmonary embolism *Study Design:* pre- and post-intervention *Methods:* Pre-intervention data were collected from January 11, 2011 to December 31st 2011, and post intervention data were collected from January 1, 2012	Academic Urban Emergency Department	*Inclusion Criteria:* patient presentation to the emergency department and clinician suspicion of acute symptomatic pulmonary embolism *Exclusion Criteria:* treatment with therapeutic doses of anticoagulants for more than 24 hours, life expectancy of less than 3 months, documented pregnancy, geographical inaccessibility precluding follow-up, younger than 18 years old, allergy to contrast agents, renal insufficiency, logistic problems, and haemodynamic instability	Clinical Decision tool intended to guide diagnostic testing for PE. No other details reported *Follow-up Time:* 12 months	Not reported

	to December 31st 2012		*Participant demographics*: **Pre-intervention:** 652 patients, mean age 67.9 years, 5.4 days of symptoms, sex distribution not reported **Post-intervention:** 711 patients, mean age 69.8 years, 4,1 days of symptoms, sex distribution not reported		
Kanaan, 2013, United States	*Objective:* To evaluate appropriate utilization rates for CT pulmonary angiography in a tertiary center emergency department before and after a health care provider educational intervention *Study Design:* pre- and post-intervention *Methods:* Retrospective review of radiology information systems database 27 days before intervention and 26 days after intervention	Single center , academic Emergency Department	*Inclusion Criteria:* Adult patients 18 years or older presenting to emergency department who had CTPA performed during emergency department visit *Exclusion Criteria:* No exclusions *Participant demographics*: **Pre-intervention:** 100 patients, mean age 47 (range 18-93), 65% female **Post-intervention:** 100 patients, mean age 49 (range 18-82), 59% female	Formal educational intervention, consisting of a 45-minute didactic lecture followed by a 30-minute question and answer session. Education session was attended by 30 emergency department residents, 20 attending physicians and 10 physician assistants. Topics included, clinical aspects, imaging and other tests for diagnosing PE, indications, contraindications and side-effects, and a summary of recent published guidelines. Emphasis on the usefulness of D-dimer testing and alternatives to CT. *Follow-up Time:* 26 days	Not applicable

Murthy, 2016, South Africa	*Objective:* To determine the impact of an electronic clinical decision support (CDS) for PE on the efficiency of CTPA utilization in a resource-limited setting. *Study Design:* Three phase intervention study *Methods:* The study was conducted in 3 phases. Phase 1: baseline observation (before December 2012); Phase 2: Introducing clinical guidelines to combine modified Well's and D-dimer tests (December 2012 – December 2013); Phase 3: Introducing CDS (in December 2013).	One 386-bed public-sector tertiary-level teaching hospital	*Inclusion Criteria:* Consecutive CTPAs performed in the respective time periods were analyzed *Exclusion Criteria:* excluded patients who were pregnant, post-partum or <18 years of age. *Participant demographics*: 424 patients (Phase 1: 149; Phase 2:174; Phase 3: 101) Mean age 48.2 years, male/female ratio 1:1.9, Inpatients 50.2%, Outpatients 49.8%	**Intervention 1:** A PE diagnostic algorithm was distributed to all hospital clinicians, outlining the combined role of the validated modified Wells score and the quantitative D-dimer test in defining the pre-test probability of PE. **Intervention 2**: Clinicians were prompted to enter the Wells score and the D-dimer test result, thereby defining the pre-test probability of PE and hence the appropriateness of the CTPA request. *Follow-up Time:* NR	Clinical guidelines explain the combined role of the validated modified Wells score and the quantitative D-dimer test in defining the pre-test probability of PE. D-dimer is done if modified Well's score <= 4. If D-dimer is negative, patient is examined for other pathology or discharged if stable. If Well's score is > 4, patient's creatinine level is measured. If it is <= 140 mmol/L CTPA is performed, otherwise VQ scan or CTPA is performed with renal support.
Ong, 2012, Australia	*Objective:* To evaluate the effect of implementing the Wells score clinical prediction tool (CPT) on rationalizing the use of CT pulmonary angiography (CTPA) for diagnosing pulmonary embolism (PE) *Study Design:* Pre- post-intervention *Methods:* A retrospective study was conducted over a 3-month period (pre-intervention) and a pre-test probability Wells score	Tertiary teaching hospital	*Inclusion Criteria:* Patients investigated with CTPA for suspected PE were enrolled. *Exclusion Criteria:* NR *Participant demographics*: 268 patients included, no demographics reported	Using Wells score, patients were stratified into pre-test probability categories. Those stratified high risk were investigated with CTPA. Low and medium-risk patients had D-dimer assays performed and were only imaged with CTPA if this was elevated. Completion of the algorithm form was required before the CT radiographers would	Diagnostic algorithm suggests to use of Wells score as a primary screening tool to stratify patients into low, intermediate or high risk of PE, and assign D-dimer and/or imaging methods accordingly.

	was assigned to each patient based on information obtained from medical records. A prospective study was conducted after a diagnostic algorithm sheet was introduced and clinicians were encouraged to use this when assessing patients for suspected PE.			perform a CTPA. Recorded data for each case included Wells score, date of CTPA, D-dimer level (if available) and final imaging result (PE or no PE). *Follow-up Time:* 7 months	
Prevedello, 2013, USA	*Objective: T*o determine whether previously documented effects of clinical decision support on CT for PE in the emergency department (ie, decreased use and increased yield) are due to a decrease in unwarranted variation. *Study Design:* Retrospective pre- post- intervention study *Methods:* Retrospective data collected from January 1, 2006 to March 31, 2009. Enrolled all patients who had PE-CT performed 18 months pre- and post-clinical decision support implementation. Intra- and inter-physician variability in yield (% PE-CT positive for acute pulmonary embolism) were assessed. Yield variability was measured using logistic regression accounting for patient characteristics.	Academic adult medical center emergency department with 60,000 annual visits	*Inclusion Criteria:* All patients presenting to the emergency department who underwent pulmonary embolism CT (PE-CT) during the 18-month periods before and after clinical decision support implementation. *Exclusion Criteria:* Examinations requested by physicians who were not present throughout the entire study period were excluded from the analysis. *Participant demographics*: **Pre-intervention**: 1524 patients, mean age 55.23 (SD 18.1) years, 65.2% female **Post-intervention**: 1349 patients, mean age 55.07 (SD 17.7) years, 62.9% female.	The intervention consisted of a clinical decision support tool for PE-CT (based on the criteria of Wells) within the institution's computerized physician order entry system. The clinical decision support required information about the level of clinical suspicion for pulmonary embolism (low, intermediate, or high) and the serum D-dimer level (not done, unknown, normal, or elevated). *Follow-up Time:* NA	Not applicable
Raja, 2015, USA	*Objective:* To assess whether implementing emergency department physician	ED of an urban level 1 adult trauma	*Inclusion Criteria:* all attending emergency physicians.	The intervention consisted of quarterly performance feedback	Not applicable

	performance feedback reports improves adherence to evidence-based guidelines for use of CT for evaluation of PE beyond that achieved with clinical decision support alone. *Study Design:* Randomized controlled trial *Methods:* Imaging CDS was deployed for all requests for CT for evaluation of PE throughout the study period. Ordering providers could ignore the evidence presented in CDS and proceed with requests for CT for evaluation of PE that deviated from evidence-based guidelines without interference. We included all attending emergency physicians and, before randomization, stratified them into quartiles by use of CT for PE in 2012. Attending physician assignment in the ED was random, with all attending physicians being equally likely to work in all areas of the ED. Attending physicians were then randomized by quartile into two groups using a random number generator; the intervention group received individualized feedback reports on adherence to evidence-based guidelines on use of CT for evaluation of PE, use (defined as number of CT examinations for PE per 1000 patients), and yield (defined as	center	*Exclusion Criteria:* both new physicians who joined the group after intervention start date and physicians who left before study completion were excluded from the analysis. *Participant demographics*: 43 attending physicians, 13 of whom (30%) were women, were included. **Control group**: 21 physicians, 29% of women, Mean age 41.2 (SD 8.6) years, Mean experience 9.2 (SD 9) years **Intervention group**: 22 physicians, 32% of women, Mean age 39.4 (SD 7.6) years, Mean experience 8.3 (SD 8.4) years	reports, sent via e-mail that displayed both individual physicians' statistics and their performance compared with anonymized results for the entire group of emergency physicians. The frequency of feedback report distribution was selected to mirror other physician performance feedback reporting initiatives at our institution. In addition, physicians were given the medical record numbers of any patients for whom the CT examinations ordered for evaluation of PE were deemed non-adherent to evidence based guidelines by CDS to facilitate individual chart review. *Follow-up Time:* NA	

	percentage of CT examinations for PE with positive findings), whereas the control group did not.				
Raja, 2012, USA	*Objective:* To determine the effect of evidence-based clinical decision support (CDS) on the use and yield of computed tomographic (CT) pulmonary angiography for acute pulmonary embolism (PE) in the emergency department (ED). *Study Design:* Pre- post-intervention *Methods:* Use (number of examinations per 1000 ED visits) and yield of CT pulmonary angiography were compared before and after CDS implementation. The authors developed and validated a natural language processing tool to identify acute PE diagnoses. Linear trend analysis was used to assess for variation in CT pulmonary angiography use. Logistic regression was used to determine variation in yield after controlling for patient demographic and clinical characteristics.	793-bed quaternary care institution with 60 000 annual ED visits.	*Inclusion Criteria:* included all adult patients presenting to the ED *Exclusion Criteria: NR* *Participant demographics*: **Pre-intervention**: 3855 patients, 65.7% female, Mean age 55.5 (SD 17.9) years **Post-intervention**: 2983 patients, 63.9% female, Mean age 55.3 (SD 17.9) years	We integrated CDS on the basis of validated decision rules into our ED radiology computerized physician order entry system (Percipio; Medicalis, San Francisco, Calif) during August 2007. *Follow-up Time:* 2 months	The CDS consisted of three rules. The first rule required that ordering clinicians choose both a D -dimer level (elevated, normal, or not evaluated) and the clinical suspicion of PE (high, intermediate, or low). The second rule displayed advice in patients with an intermediate or low level of suspicion in whom a D –dimer assay was not performed ("measuring a D -dimer value in patients with a low and/or intermediate clinical suspicion of PE is an appropriate first step in the work-up of acute PE and will exclude the need for CT pulmonary angiography in some patients"). The third rule displayed a second piece of advice in patients with a normal D -dimer level and intermediate or low suspicion for PE ("based on current evidence as well as our experience at Brigham and Women's Hospital, diagnosing an acute PE with CT pulmonary angiography in low- or intermediate-risk patients with a normal D -dimer level is extremely unlikely"). At each stage, clinicians could either cancel the imaging order or ignore the advice.
Stein,	*Objective:* To determine	A large	*Inclusion Criteria:* Patients with	Two hour-long	Not applicable

2010, USA	whether the radiation exposure to patients with suspected pulmonary embolism (PE) could be decreased by safely increasing the use of ventilation–perfusion (V/Q) scanning and decreasing the use of CT pulmonary angiography (CTPA) through an educational intervention. *Study Design:* Pre- post-intervention *Methods:* Collaborative educational seminars were held among the radiology, nuclear medicine, and emergency medicine departments in December 2006 and January 2007 regarding the radiation dose and accuracies of V/Q scanning and CTPA for diagnosing PE. To reduce radiation exposure, an imaging algorithm was introduced in which emergency department patients with a clinical suspicion of PE underwent chest radiography. If the chest radiograph was normal, V/Q scanning was recommended, otherwise CTPA was recommended. We retrospectively tallied the number and results of CTPA and V/Q scanning and calculated mean radiation effective dose before and after the intervention. False-negative	urban academic medical center	clinically suspected PE *Exclusion Criteria:* NR *Participant demographics*: **Pre-intervention**: CT: 66% women, mean age 55 years VQ: 71% women, mean age 54.7 years **Post-intervention**: CT: 65.9% women, mean age 56.7 years VQ: 74% women, mean age 50.8 years	seminars were held with the available emergency department staff, including residents and attending physicians. It was recommended to the emergency department clinicians that stable patients with a clinical suspicion of PE should initially be imaged with chest radiography. If the chest radiography findings were normal and further imaging for suspected PE was deemed appropriate by clinical assessment, the emergency department staff was advised to request a V/Q scan. If the chest radiograph showed a pleural or parenchymal abnormality, CTPA was recommended. If either examination was equivocal or the imaging results were discordant with the clinical impression, the emergency department staff was advised to request the alternative test in addition. The algorithm was provided to the emergency department staff as a handout, which resulted	

	findings were defined as subsequent thromboembolism within 90 days.			in a collaborative, consultative approach between the imaging services and the emergency department staff. *Follow-up Time:* 90 days	
Walen, 2016, The Netherlands	*Objective:* To determine if mandatory adherence to a diagnostic protocol increases the rate of CT pulmonary angiographies (CTPAs) positive for pulmonary embolism (PE). *Study Design:* Prospective observational *Methods:* Data was prospectively collected from January 2014 to June 3, 2014 The percentage of positive CTPA scans was calculated and compared with previous cohort (Walen et al. Insights Imaging). Odds ratios were calculated as a measure of association between dichotomous variables and CTPA findings.	NR	*Inclusion Criteria:* all patients with suspected PE requiring a CTPA scan. *Exclusion Criteria:* NR *Participant demographics*: **All patients**: 53.4% women, mean age 64 (range 49 – 73) years	As an intervention every physician in our hospital requesting a CTPA for pulmonary embolism was asked to document Wells-scores on the request form and—if available—to document D-dimer. Special templates of the request form with a pre-printed Wells scoring table were distributed among requesting physicians. When the required information was lacking on the request forms our diagnostic radiographers urged the requesting doctor to provide the necessary clinical data. However, no scans were refused. If a scan was nevertheless performed without the clinical data documented on the request form, the scores were retrospectively obtained. Electronic	Not applicable

				and paper medical files were searched for clinical characteristics and relevant medical history. *Follow-up Time:* NA	

Table C2: Quality Assessment using Downs and Blacks Checklist

Author (Year)	Agarwal[1] 28	Booke[12] 6	Dunne[12] 7	Geeting[125]	Harding[1] 32	Jimenez[129]	Kanaan[1] 33	Murthy[136]	Ong[135]	Prevedello[1] 30	Raja[138]	Raja[131]	Stein[134]	Walen[137]
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the characteristics of the patients included in the study clearly described ?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No	No	Yes	Yes	No	No	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
Have all important adverse events that may be a consequence of the intervention been	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes

reported?														
Have the characteristics of patients lost to follow-up been described?	Yes	No	No	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	No	NA
Have actual probability values been reported for the main outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Was an attempt made to blind study subjects to the intervention they have received ?	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	No	No	No	No	No	No	Unclear	Yes	No	No	No	No	Yes

If any of the results of the study were based on "data dredging", was this made clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No

Were study subjects randomized to intervention groups?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Unclear	NA	NA	NA
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unclear	Unclear	Yes	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Were losses of patients to follow-up taken into account?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No	NA
Q27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	16	13	16	16	15	13	14	13	9	12	17	11	12	13

NA: Not applicable

Appendix D: **Cost-Effectiveness and Budget Impact Analysis**

Search Strategy

MEDLINE March 10, 2017

1 embolism/ or pulmonary embolism/
2 thromboembolism/ (
3 thrombosis/
4 embolism, paradoxical/ or venous thromboembolism/
5 venous thrombosis/ or thrombophlebitis/ or upper extremity deep vein thrombosis/
6 (embolus or embolism?).tw.
7 thromboembolism?.tw.
8 (thrombosis or thrombosus or thromboses).tw.
9 (phlebothromboses or phlebothrombosis).tw.
10 (thrombophlebitis or thrombophlebitides).tw.
11 phlegmasia alba dolens.tw.
12 paget schroetter syndrome.tw.
13 or/1-12
14 Diagnosis/
15 di.fs. [Diagnosis]
16 sensitiv$.mp.
17 diagnos$.mp.
18 (predictive value or accurac$).mp.
19 "Sensitivity and Specificity"/
20 or/14-19
21 13 and 20
22 tomography/
23 magnetic resonance imaging/ or cholangiopancreatography, magnetic resonance/ or diffusion magnetic resonance imaging/ or echo-planar imaging/ or magnetic resonance angiography/ or magnetic resonance imaging, cine/
24 tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
25 tomography, emission-computed/ or positron-emission tomography/ or tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
26 tomography, optical/ or tomography, optical coherence/
27 tomography, x-ray/ or tomography, x-ray computed/ or cone-beam computed tomography/ or spiral cone-beam computed tomography/ or four-dimensional computed tomography/ or tomography, spiral computed/ or x-ray microtomography/
28 computed tomography.tw.
29 ((helical or spiral or multislice) adj5 tomography).tw.
30 spiral CT.tw.
31 or/22-30
32 13 and 31
33 Ultrasonography/
34 ((leg or compression) adj5 (ultrasound or ultrasonography)).tw.
35 Ultrasonography, Doppler/

36 us.fs. [Ultrasonography]
37 or/33-36
38 13 and 37
39 angiography/ or angiocardiography/ or angiography, digital subtraction/ or aortography/ or cerebral angiography/ or cineangiography/ or coronary angiography/ or phlebography/ or portography/
40 pulmonary angiography.mp.
41 or/39-40
42 13 and 41
43 ventilation perfusion scintigraphy.tw.
44 "Perfusion Imaging"/
45 myocardial perfusion imaging/
46 ri.fs. [Radionuclide Imaging]
47 ra.fs. [Radiography]
48 "V/P(SCAN)".tw.
49 MDCT.tw.
50 "V/P(PLANAR)".tw.
51 "V/Q".tw.
52 ((lung or ventilation or perfusion) adj5 scintigraphy).tw.
53 or/43-52
54 13 and 53
55 Clinical Laboratory Techniques/
56 "Diagnostic Techniques and Procedures"/
57 Fibrin Fibrinogen Degradation Products/
58 D-dimer.mp.
59 Biological Markers/
60 immunoassay/
61 fluoroimmunoassay/ or fluorescence polarization immunoassay/
62 immunoblotting/ or blotting, western/ or blotting, far-western/
63 immunochromatography/
64 immunoenzyme techniques/ or enzyme-linked immunosorbent assay/ or enzyme-linked immunospot assay/ or enzyme multiplied immunoassay technique/
65 immunosorbent techniques/
66 radioallergosorbent test/ or radioimmunoprecipitation assay/ or radioimmunosorbent test/
67 radioimmunoassay/ or immunoradiometric assay/
68 ELISA.tw.
69 or/55-68
70 13 and 69
71 ((Well$2 or Geneva) adj3 (score? or criteria or method?)).tw.
72 clinical probability.tw.
73 probability assessment.mp.
74 or/71-73
75 13 and 74
76 exp economics/
77 quality of life/
78 value of life/

79 quality-adjusted life years/
80 models, economic/
81 markov chains/
82 monte carlo method/
83 decision tree/
84 economic$.tw.
85 ec.fs.
86 (cost? or costing? or costly or costed).tw.
87 (price? or pricing?).tw.
88 (pharmacoeconomic? or (pharmaco adj economic?)).tw.
89 budget$.tw.
90 expenditure$.tw.
91 (value adj1 (money or monetary)).tw.
92 (fee or fees).tw.
93 "quality of life".tw.
94 qol?.tw.
95 hrqol?.tw.
96 "quality adjusted life year?".tw.
97 qaly?.tw.
98 cba.tw.
99 cea.tw.
100 cua.tw.
101 markov$.tw.
102 (monte adj carlo).tw.
103 (decision adj2 (tree? or analys$ or model$)).tw.
104 utilit$.tw.
105 ((clinical or critical or patient) adj (path? or pathway?)).tw.
106 (managed adj2 (care or network)).tw.
107 or/76-106
108 13 and 20 and 107
109 13 and 31 and 107
110 13 and 37 and 107
111 13 and 41 and 107
112 13 and 53 and 107
113 13 and 69 and 107
114 13 and 74 and 107
115 or/108-114
116 comment/ or editorial/ or letter/
117 115 not 116
118 limit 117 to yr="1990 -Current"
119 limit 118 to English language
120 limit 119 to humans
121 119 not 120
122 from 121 keep 7,12,15-16,18,23,29,36
123 120 or 122 [English]
124 118 not 119 [Non-English]