# *DiPEP*

## DiPEP: Diagnosis of Pulmonary Embolism (PE) in Pregnancy

**DiPEP RESEARCH PROTOCOL**
**(Version 6.1) 23 November 2016**

**REC reference:**
**HTA reference:**       13/21/01
**ISRCTN:**       21245595

**Authorised by:**

# Diagnosis of Pulmonary Embolism (PE) in Pregnancy (DiPEP)

This document describes the DiPEP study, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

## Contents

## Abbreviations

| | |
|---|---|
| A&E | Accident and Emergency |
| BMI | Body Mass Index |
| BSH | British Society for Haematology |
| CRF | Case report form |
| CTPA | Computerised tomography pulmonary angiogram |
| CTRU | Clinical trials research unit |
| DMEC | Data Monitoring and Ethics Committee |
| DVT | Deep vein thrombosis |
| ECG | Electrocardiogram |
| EQ5D | European Quality of Life Measure (5 Dimensions) |
| ESC | European Society of Cardiology |
| GCP | Good Clinical Practice |
| GDC | Guideline Development Group |
| GSTT | Guy's and St Thomas′ (NHS Foundation Trust) |
| HTA | Health Technology Assessment |
| IRAS | Integrated Research Approval System |
| LREC | Local Research Ethics Committee |
| MBRRACE-UK | Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK |
| MRI | Magnetic Resonance Imaging |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIGB | National Information Governance Board |
| NIHR | National Institute for Health Research |
| PE | Pulmonary embolism |
| PERC | Pulmonary Embolism Rule Out Criteria |
| PI | Principal Investigator |
| QALY | Quality adjusted life year |
| R&D | Research and Development |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| REC | Research ethics committee |
| ROC | Receiving Operator Characteristic |
| SECF | Sheffield Emergency Care Forum |
| SMR2 | Scottish Morbidity Record 2 |
| SOP | Standard operating procedure |
| SSL/TLS | Secure Sockets Layer/Transport Layer Security |
| UKOSS | UK Obstetric Surveillance System |
| VQ | Ventilation-perfusion scan |
| VTE | Venous thromboembolism |

## Definition of terms

| | |
|---|---|
| Biomarker | A biological feature that can be used to measure the presence or progress of disease or the effects of treatment |
| Discrete event simulation | The process of codifying the behaviour of a complex system as an ordered sequence of well-defined events |
| Meta-modelling | A definition of the constructs and rules needed for creating models |
| Pulmonary embolism | An obstruction of a blood vessel in the lungs, usually due to a blood clot |
| Sensitivity | The ability of a test to correctly identify patients with a disease |
| Specificity | The ability of a test to correctly identify patients without a disease |

# General information

**Sponsor**

Erica Wallis
Clinical Research Office
Sheffield Teaching Hospital NHS Foundation Trust
D Floor, Royal Hallamshire Hospital,
Glossop Road,
Sheffield
S10 2JF
Tel: +44 (0) 114 2265931
Fax: +44 (0) 114 2265937
Email: Erica.wallis@sth.nhs.uk

**Chief Investigator**

Prof Steve Goodacre
Professor of Emergency Medicine
Medical Care Research Unit
ScHARR
University of Sheffield
Regent Court
30 Regent Street
S1 4DA
Tel: +44 (0) 114 2220842
Fax: +44 (0) 114 2220749
Email: s.goodacre@sheffield.ac.uk

**Clinical trials support and management (including study monitoring)**

Kimberley Horspool
Trial Manager
Sheffield Clinical Trials Research Unit
ScHARR
University of Sheffield
Regent Court
30 Regent Street
Sheffield S1 4DA
Tel: +44 (0) 114 222 4348
Fax: +44 (0) 114 222 0870
Email: k.horspool@sheffield.ac.uk

**UKOSS lead**

Prof Marian Knight
NIHR Research Professor
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Email: marian.knight@npeu.ox.ac.uk

**Biomarker study lead**

Prof Beverley Hunt
Professor of Thrombosis and Haemostasis and Director of the Haemostasis Research Unit
Guy's & St Thomas's NHS Foundation Trust
Departments of Haematology and Rheumatology
Tel: +44 (0) 20 7188 2736
Fax: +44 (0) 20 7188 2717
Email: Beverley.Hunt@gstt.nhs.uk

**Trial statistician**

Prof Michael Campbell
Sheffield Clinical Trials Research Unit
ScHARR
University of Sheffield
Regent Court
30 Regent Street
S1 4DA
Tel: +44 (0) 114 2220839
Fax: +44 (0) 114 222 0870
Email: m.j.campbell@sheffield.ac.uk

## Protocol amendments since Version 1

| Author | Reviewer | Previous version number | Summary of changes |
|---|---|---|---|
| K.Horspool | S.Goodacre | Version 1 | Defining postpartum, diagnosed PE exclusion criteria, diagnostic imagining includes lower limb venous imaging, definition of complications, clarification of women already with PE diagnosed, inclusion and exclusion criteria for DVT participants, appropriately trained clinicians to collect data, section 5.1.4, section 5.1.7, biomarker study to include CRP, clarification of DVT and Suspected PE in the analysis, additional secondary analysis to test the performance of an expert consensus CDR |
| K.Horspool | S.Goodacre | Version 2 | Clarification of additional blood sample for Suspected PE. |
| K.Horspool | S.Goodacre | Version 3 | Aged <16 years added as exclusion criteria, definition of postpartum amended, clarified that women who have received diagnostic imaging for suspected PE can be recruited if they are still in hospital |
| K Horspool | S. Goodacre | Version 4 | Multiple presentations is addressed in data collection and analysis, new TSC member added, Increased number of follow ups attempts to collect patient reported data |
| K Horspool | S. Goodacre | Version 5 | Data collection by GP and GP patient notes for women where PE and adverse events cannot be ruled out, revised recruitment target to 325 for Suspected PE of to account for attrition in the primary outcome data, updated projections on number with confirmed PE based on the original 2% positive estimate participating sites revised to 11, updated an incorrect public representative name |
| B Hunt | | Version 6 | Addition of new assay and change in D-dimer assay |

## Study Summary

***Design:*** (1) Primary research involving cases identified through the UKOSS research platform and controls identified through a prospective study of pregnant and postpartum women with suspected PE. (2) Decision-analysis modelling of effectiveness, cost-effectiveness and value of information.

***Setting:*** Hospital emergency departments and maternity units.

***Strategy for reviewing literature:*** We will undertake systematic searches for any studies of clinical predictors or biomarkers for PE in pregnancy and key parameters in the decision-analysis model.

***Target population:*** We will (a) identify pregnant and postpartum women with diagnosed PE from all UK hospitals using the UKOSS research platform and (b) recruit pregnant and postpartum women with suspected PE from 8-20 hospitals over 18 months. We will exclude those who did not present with suspected PE from the former group and those unable to consent, requiring resuscitation or with an existing diagnosis of PE from the latter group.

***Health technologies being assessed:*** Clinical predictors and biomarkers for PE, and diagnostic strategies (including clinical prediction rules) to select pregnant or postpartum women for imaging.

***Measurement of costs and outcomes:*** The nominated clinician for UKOSS will collect data from women with diagnosed PE detailing clinical variables, blood tests results, diagnostic imaging, treatment and adverse events. Research nurses will collect standardised clinical data and a blood sample at enrolment from women with suspected PE and review hospital records at 30 days to record the results of diagnostic imaging, treatment and adverse events. A questionnaire will then be sent to record adverse events, health care use and health utility. Two independent assessors, blind to clinical predictors and blood results, will classify participants as having PE using diagnostic imaging results and details of serious adverse events.

Sensitivities and specificities of clinical predictors, biomarkers and diagnostic strategies will be estimated using data from cases and controls respectively. Decision-analysis modelling will be used to estimate costs incurred and expected outcomes from thromboembolism, bleeding and radiation exposure if a hypothetical cohort of pregnant or postpartum women were investigated for suspected PE using different strategies, including no imaging, selective imaging and imaging for all. Outcomes will be modelled to estimate the quality-adjusted life years (QALYs) accrued by each strategy and the incremental cost per QALY gained by each strategy compared to the next most effective alternative.

***Sample size:*** Data will be collected from 150 women with diagnosed PE and 325 women with suspected PE, resulting in about 155 cases and 319 controls. This will allow estimation of sensitivity or specificity of 90% with standard errors of about 2.5% and 2.0% respectively.

***Project timetables including recruitment rate:***
Months 1-6: Preparation, ethics and R&D approval, finalise data collection

Months 7-24: Primary data collection from UKOSS cases (all UK hospitals) and women with suspected PE (8 hospitals, 25 per hospital per year), development of the model

Months 25-30: Follow-up, analysis, modelling and writing-up

Expertise in team: The team includes international experts in obstetric medicine, haematology, epidemiology, emergency medicine, vascular radiology, health economic modelling and statistics.

# 1. Introduction

*Background and Rationale*

PE is a leading cause of death in pregnancy and postpartum that affects women who would otherwise expect to have long life expectancy in full health. Furthermore, the outcome for the fetus is dependent on the outcome for the mother. Patients with appropriately diagnosed and treated PE have a low risk of adverse outcome, so accurate diagnosis can result in substantial benefits. However, the investigations used to diagnose PE (diagnostic imaging with VQ scanning or CT pulmonary angiography) carry risks of radiation exposure, reaction to contrast media and false positive diagnosis, are inconvenient for patients and incur costs for the health services. Clinicians therefore face a difficult choice when deciding how to investigate suspected PE in pregnant and postpartum women, between risking the potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking iatrogenic harm to women without PE if imaging is over-used.

*Current practice*

Guidelines from the Royal College of Obstetricians and Gynaecologists (2010) and American Thoracic Society (Leung 2011) recommend that pregnant or postpartum women with suspected PE should all receive diagnostic imaging, while guidelines from the European Society of Cardiology (Torbicki 2008) suggest a possible role for D-dimer in selecting patients. Current data suggest that use of an unselective approach is resulting in a low prevalence of PE among those investigated. The most recent studies of suspected PE in pregnancy report prevalence of between 1.4 and 4.2% (Bourjeilly 2012, Abele 2013, Nijkeuter 2013, Cutts 2014), while audit data from Sheffield Teaching Hospitals NHS Foundation Trust show a prevalence of 2% among those undergoing imaging. We therefore appear to be exposing 50 women (and foetuses in pregnant women) to the risks of diagnostic imaging for every one with PE who is able to benefit from diagnosis and treatment.

These recommendations for pregnant and postpartum women contrast with National Institute for Health and Care Excellence (NICE) guidelines for the general (non-pregnant) population with suspected PE, for whom diagnostic imaging is selectively used based upon structured clinical assessment and D-dimer measurement (NICE 2012). The diagnostic accuracy of clinical features, clinical prediction scores and D-dimer is well established in the general population with suspected PE, but is uncertain in pregnant and postpartum women. Clinical assessment or biomarkers could play an important role in selecting pregnant or postpartum women with suspected PE for imaging, but evidence of their diagnostic accuracy is required.

*Literature review*

We systematically searched electronic databases for diagnostic studies of pregnant or postpartum women investigated for suspected PE using the search terms Pregnancy and Pulmonary Embolism [Diagnosis], Pulmonary Embolism [Radiography] or Pulmonary Embolism [Radionuclide Imaging]. We screened 198 citations and identified 11 relevant articles. These are outlined in table 1, along with a conference abstract and paper in press identified.

**Table 1: Diagnostic studies of pregnant or postpartum women with suspected PE**

| Study | Country | Population | Index tests | Reference standard | Main findings |
|---|---|---|---|---|---|
| Balan 1997 | UK | 82 pregnant women, one hospital, 5 years | None | VQ scan | 31 (38%) normal<br>19 (23%) low probability<br>14 (17%) intermediate<br>18 (22%) high |
| Chan 2002 | Canada | 113 pregnant women, 2 hospitals, 4 & 10 years | None | VQ scan | 83 (73.5%) normal<br>28 (24.8%) nondiagnostic<br>2 (1.8%) high probability |
| Scarsbrook 2007 | UK | 94 pregnant women, 1 hospital, 5 years | None | VQ scan | 89 (92%) normal<br>7 (7%) nondiagnostic<br>1 (1%) high probability |
| Cahill 2009 | USA | 304 pregnant or postpartum, 1 hospital, 5 years | Clinical features[1] | 108 CTPA & 196 VQ scan | 18 (5.9%) diagnosed PE<br>Low oxygen saturation and chest pain predicted PE, other features did not |
| Damodram 2009 | UK | 37 pregnant women, 1 hospital, 4 years | D-dimer | VQ scan | 13 (35%) low probability<br>24 (65%) intermediate or high<br>D-dimer sensitivity 73%, specificity 15% |
| Shahir 2010 | USA | 199 pregnant women, 1 hospital, 8 years | None | 106 CTPA & 99 VQ scan | CTPA: 4/106 (3.7%) PE<br>VQ scans: 0 high probability, 2 intermediate, 19 low, 14 very low, 63 normal, 1 inconclusive |
| Deutsch 2010 | USA | 102 pregnant or postpartum women, 1 hospital, 7 years | Clinical features[2] | CTPA | CTPA: 13/102 (13%) PE<br>Only chest pain predicted PE |
| Hassanin 2011 | Egypt | 60 postpartum women, 1 hospital, years not reported | D-dimer | CTPA | 4 (6.6%) PE<br>D-dimer positive in all cases |
| O'Connor 2011 | Ireland | 125 pregnant or postpartum women, 1 hospital, 5 years | Modified Wells score<br>D-dimer<br>Blood gas<br>ECG | CTPA | CTPA: 5/103 (5%) PE<br>Modified Wells 100% sensitive & 90% specific<br>D-dimer 0% and 74% |
| Bourjeilly 2012 | USA | 343 pregnant women, 1 | Clinical features[3] | CTPA | 8 (2.3%) PE<br>No association found |

| | | hospital, 5 years | | | between clinical features and PE |
|---|---|---|---|---|---|
| Abele 2013 | Canada | 74 pregnant women, 3 hospitals, 1.5 years | None | Perfusion scan & CTPA if abnormal | 61 (82.4%) normal perfusion 13 (17.6%) abnormal – 1 (1.4%) PE on CTPA |
| Nijkeuter 2013 (abstract) | Netherlands | 149 pregnant women, 3 hospitals, 9 years | None | CTPA | 6 (4.2%) PE 8 (5.6%) inconclusive 129 (90.2%) normal |
| Cutts 2014 (in press) | UK & Australia | 183 pregnant women, 2 hospitals, 4 years | Modified Wells score | VQ scan | 4 (2%) high probability 6 (3%) nondiagnostic 173 (95%) normal D-dimer positive in 48/51 Modified Wells score predicted PE |

[1]Chest pain, dyspnea, heart rate, oxygen saturation, A-a gradient
[2]Chest pain, dyspnea, heart rate, respiratory rate, blood pressure, oxygen saturation, A-a gradient
[3]Chest pain, dyspnea, pleuritic chest pain, haemoptysis, cough, DVT signs, wheeze, pleural rub, heart rate, respiratory rate, systolic blood pressure

Studies were generally small and had low prevalence of PE, particularly in recent cohorts of unselected patients. Six of the studies focussed on the results of imaging rather than evaluating alternative diagnostic methods. Those that evaluated other diagnostic methods had limited power to detect an association with a reference standard diagnosis of PE. Cahill et al (2009) found that chest pain and low oxygen saturation were associated with a diagnosis of PE, but other features (dyspnoea, tachycardia, A-a gradient) showed no evidence of association. Deutsch et al (2010) also found that chest pain showed some association with a diagnosis of PE, while other features (dyspnea, heart rate, respiratory rate, blood pressure, oxygen saturation, A-a gradient) did not. Bourjeily et al (2012) found no association between dyspnea, chest pain, pleuritic chest pain, haemoptysis, cough, DVT signs, wheeze, pleural rub, heart rate, respiratory rate or systolic blood pressure and a diagnosis of PE.

Two studies have suggested that the modified Wells score, which was developed to diagnose PE in the non-pregnant population, may be useful in pregnant or postpartum women. O'Connor et al (2011) reported that a modified Wells score of six or greater (PE likely) has sensitivity of 100% and specificity of 90% for PE, while Cutts et al (2014) reported sensitivity of 100% (95% confidence interval 40 to 100%) and specificity of 60% (52 to 67%). The wide confidence intervals for sensitivity mean that further research is required. Other clinical prediction rules, such as the Geneva score and PERC rule, have not yet been tested in pregnant or postpartum women with suspected PE.

Studies of D-dimer in pregnant and postpartum women (Damodram 2009, Hasanin 2011, O'Connor 2011, Cutts 2014) suggest that high levels of positivity at conventional thresholds limit the diagnostic value of this test. However, indirect evidence from studies of D-dimer for suspected DVT in pregnancy suggests potential diagnostic value. Chan et al (2007) reported 100% sensitivity (95% confidence interval 77 to 100%) and 60% specificity (52 to 68%) for the qualitative SimpliRED d-dimer in suspected DVT, and although another study of five commercially available assays (Chan 2010) reported specificities ranging from 6 to 23%, further analysis suggested that using a higher threshold for positivity could improve sensitivity without compromising specificity.

Other studies have compared pregnant or postpartum women with PE to an asymptomatic control group to identify risk factors for PE in pregnancy. Although not directly applicable to diagnosis of suspected PE these studies identify variables that may be diagnostically useful. Knight et al (2008) compared women with antenatal PE identified through UKOSS research platform to pregnant controls and showed that multiparity and body mass index (BMI) were independent predictors of developing PE. Kane et al (2013) used cases identified by the Scottish Morbidity Record 2 (SMR2) to show that women aged over 35, with previous venous thromboembolism (VTE), pre-eclampsia, antenatal haemorrhage or postnatal haemorrhage were more likely to develop PE than those without these characteristics. Henriksson et al (2013) showed that VTE is associated with pregnancy following in vitro fertilisation. Sultan et al (2013) linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care records to show that BMI, complications of pregnancy (pre-eclampsia, antenatal or postnatal haemorrhage, diabetes, hyperemesis), co-morbidities (varicose veins, cardiac disease, hypertension) and recent hospital admission were associated with an increased risk of developing PE.

### Need for further research
Existing research suggests that clinical assessment, clinical prediction rules and/or D-dimer measurement could be used to select women for imaging but more precise estimates of diagnostic value are needed before a selective strategy can be recommended. Furthermore, the appropriate use of clinical assessment or biomarkers to select women for imaging can only be determined by explicitly weighing the risks, costs and benefits of different strategies.

We will update our literature search when data collection forms for the study are finalised and use expert opinion to identify other potential clinical predictors that currently lack supporting evidence, such as gestational age, other symptoms (chest pain, dyspnoea, syncope, palpitations), other risk factors (family history, thrombophilia, sickle cell trait, long-haul travel), examination findings (respiratory rate, blood pressure, temperature, chest auscultation, abdominal examination) and routine investigations (ECG, chest radiography).

We also plan to explore the accuracy of D-dimer with a higher (pregnancy-specific) threshold for positivity and evaluate biomarkers that are not currently used but have potential diagnostic value for PE in pregnant and postpartum women. Plasma D-dimers are specific cross-linked fibrin derivatives produced when fibrin is degraded by plasmin, elevated levels indicating thrombolysis. While highly sensitive for VTE, they are insufficiently specific to make a positive diagnosis as they are elevated in other conditions such as the end of pregnancy, pre-eclampsia, infections, malignancy and postoperative states, but given the present diagnostic paradigm, the potential importance of an exclusionary test that reduces the need for imaging is clear. There is some evidence that using a higher threshold for positivity can improve D-dimer specificity in pregnancy without compromising sensitivity (Chan 2010).

We have conducted a literature search on potential biomarkers both in and outside of pregnancy and also utilised our experts understanding of the pathophysiology of PE. We plan to measure the following biomarkers in addition to D-dimer: cardiac troponin I, B-type natriuretic peptide, prothrombin fragment 1+2, plasmin-antiplasmin complexes, prothrombin time, activated partial thromboplastin time (APTT) and Clauss fibrinogen levels.

### Target population
*Diagnosed PE*: The UKOSS research platform will be used to identify 150 pregnant or postpartum woman diagnosed with PE in the UK after presentation with suspected PE.

*Suspected PE*: We will recruit 325 pregnant or postpartum women (anticipated 163 pregnant and 162 postpartum) presenting with suspected PE across 11 participating hospitals. We anticipate that98% (N~319) will have no confirmed diagnosis of PE and will constitute the control group. Those with a diagnosis of PE confirmed (N~6) will be analysed with the cases.

### *Setting/context*
*Diagnosed PE:* UKOSS collects data from all UK hospitals with a consultant-led maternity unit. The cases may present to the health service through a variety of routes, depending upon local practice, but will ultimately be the responsibility of the obstetric services, and thus women who have a PE at any gestation will ultimately be identified whatever their route of presentation provided their pregnancy is ongoing.

*Suspected PE:* Pregnant and postpartum women with suspected PE are investigated in secondary care but may follow a variety of different pathways depending upon local practice. The eight participating hospitals will be selected to reflect this variation but in each case recruitment will be targeted at the location at which the decision to undertake diagnostic imaging is made, whether that is the emergency department, medical assessment unit or maternity unit.

### Health technologies being assessed
We will assess health technologies that can be used to select pregnant or postpartum women with suspected PE for diagnostic imaging. This will include technologies validated for use in the non-pregnant population with suspected PE (the Wells criteria, Geneva score, PERC rule and D-dimer) and clinical variables known to predict PE in pregnant or postpartum women. Our initial literature review for this study has identified a number of potential clinical variables, biomarkers and clinical prediction rules that could be used to select women for diagnostic imaging (see table 2).

### Table 2: Potential clinical predictors and biomarkers for PE in pregnant and postpartum women

| Variable | Source |
|---|---|
| Age | 2,3 |
| Body mass index | 2 |
| Parity | 2 |
| Previous DVT or PE | 2,3 |
| Complications of pregnancy (pre-eclampsia, haemorrhage, diabetes, hyperemesis) | 2 |
| Co-morbidities (varicose veins, cardiac disease, hypertension) | 2 |
| Hospital admission | 2 |
| Recent surgery or immobilization | 3 |
| Malignancy | 3 |
| Heart rate | 3 |
| Clinical signs of DVT | 3 |
| Haemoptysis | 3 |
| Oxygen saturation | 1 |
| D-dimer | 1,3 |

1: Diagnostic studies of suspected PE in pregnancy (see table 1)
2: Studies predicting risk factors for developing PE in pregnancy (Knight 2008, Kane 2013, Henriksson 2013, Sultan 2013)
3: Wells, Geneva and PERC clinical prediction scores for suspected PE in non-pregnant patients

We will conduct this trial in compliance with the protocol and GCP requirements

# 2. Aims and objectives

This study aims to (a) estimate the diagnostic accuracy, effectiveness and cost-effectiveness of strategies (including clinical prediction rules) for selecting pregnant or postpartum women with suspected PE for imaging, and (b) determine the feasibility and value of information of further prospective research.

Specific objectives:
1. To estimate the sensitivity of clinical variables, existing prediction rules (Wells, Geneva and PERC) and D-dimer for PE diagnosed in pregnant women
2. To estimate the specificity of clinical variables, existing prediction rules and D-dimer in pregnant and postpartum women with suspected PE but negative diagnostic imaging
3. To develop a new clinical prediction rule or modify an existing rule to achieve optimal sensitivity and specificity
4. To explore the potential diagnostic value of alternative biomarkers for VTE in pregnant and postpartum women and explore the use of D-dimer with a pregnancy-specific threshold for positivity
5. To determine the feasibility of using a prospective cohort design to validate a new clinical prediction rule or biomarker
6. To estimate the effectiveness of different strategies, in terms of adverse outcomes from thromboembolism, bleeding and radiation exposure, and cost effectiveness, measured as the incremental cost per quality-adjusted life year (QALY)
7. To estimate the value of information associated with further research

## 3. Study Design

The project comprises three main elements and will take 30 months to complete: (1) A case control study (2) A biomarker study. (3) Decision-analysis modelling of effectiveness, cost-effectiveness and value of information In addition, the recruitment rate to the prospective part of the case control study will be used to determine the feasibility of a future cohort study.
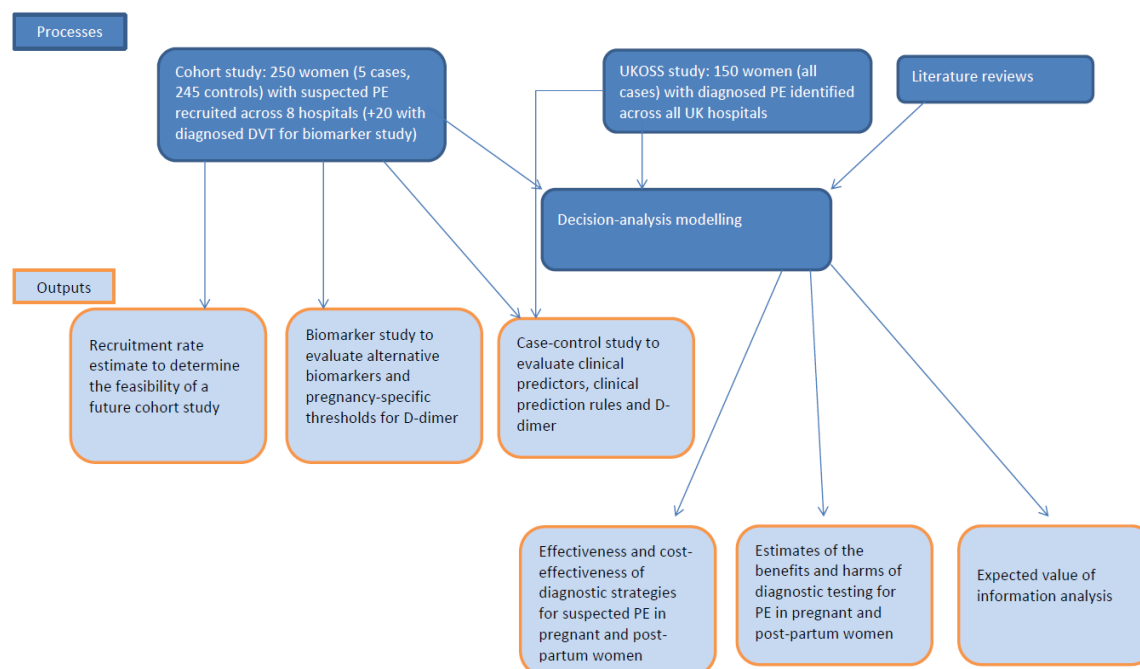


**Figure 1: Summary of the processes and outputs of the project**

**3.1 A case-control study** will address objectives 1-3 above. Cases will be women with diagnosed PE who are retrospectively identified through UKOSS, a UK-wide obstetric surveillance system that has been set up to conduct research on uncommon disorders of pregnancy. This method has been used successfully in a previous study and full details of the UKOSS methods are available at https://www.npeu.ox.ac.uk/ukoss/methodology. Controls will be identified through a prospective study of pregnant or postpartum women presenting to eight hospitals with suspected PE, of whom we anticipate 98% will have no PE diagnosed. Those diagnosed with PE will be analysed as cases.

### *Why are we not proposing a prospective cohort study?*
Primary research is required to improve our estimates of the diagnostic accuracy of clinical assessment and biomarkers. Ideally this would involve a prospective cohort study and would culminate in development and validation of a clinical prediction rule, as suggested in the commissioning brief. However, existing data suggest that this cannot be undertaken within an acceptable timeframe or budget. Data from UKOSS (Knight 2008) suggest an incidence of 1.3 per 10,000 maternities for antenatal pulmonary embolism (PE), while data from the Scottish Morbidity Record (SMR2) (Kane 2013) suggest a combined incidence of 2.0 per 10,000 maternities for antenatal and postnatal PE. With 723,913 live births in England and Wales in 2011 these data suggest 94 cases of antenatal PE or 145 cases of antenatal or postnatal PE per year. Thus a typical hospital would only see one case of PE in pregnant or postpartum women per year. Recent studies identified in our literature review confirm a rate of one or two cases per hospital per year (Deutsch 2010, Shahir 2010, O'Connor 2011, Bourjeilly 2012, Abele 2013, Nijkeuter 2013, Cutts 2014). Prospective derivation of a clinical prediction rule would require 80 cases with PE and validation a further 40. With a prevalence of PE of 2% in suspected cases undergoing investigation the total sample sizes for derivation and validation cohorts would be 4000 and 2000 respectively. This would require 50 hospitals to recruit for 4 years to achieve the derivation sample, and a further 1.6 years for the validation sample, assuming a 50% recruitment rate. Even if we could keep costs to £1000 per patient recruited this study would cost £6million.

### *Rationale for case control design*
A case-control design offers an alternative when the low prevalence of disease makes a cohort design unfeasible or unacceptably inefficient. Identification of women with the diagnosis of interest (PE in pregnancy or postpartum) allows us recruit sufficient numbers with PE to make reasonably precise estimates of sensitivity. Imprecision in the estimates of sensitivity have been the main limitation of previous studies and the main reason why selective strategies for imaging have not been implemented.

The case-control design carries an increased risk of bias compared to the cohort design (Lijmer 1999), but this will be reduced by ensuring that the control group is a representative sample of women with suspected PE who have negative imaging and that the cases are a representative sample of women presenting with suspected PE who are diagnosed and treated for PE.

Secondary research in the form of decision-analysis modelling is required to explicitly weigh the costs, risks and benefits of different strategies for selecting women for diagnostic imaging. This allows us to estimate how diagnostic tests lead to differences in clinically meaningful outcomes. Decision-analysis modelling is particularly important in this situation, when the best method of estimating diagnostic parameters (a cohort study) is not feasible. Decision-analysis modelling allows us to explore the potential impact of uncertainty on our findings, such as uncertainty associated with potential design-related bias. Value of information analysis can then be undertaken to determine

whether further research would be worthwhile to obtain more accurate or precise estimates of diagnostic accuracy.

**3.2 A biomarker study** will address objective 4. This will involve the prospectively identified women with suspected PE (N~319), ~6 women identified prospectively who are diagnosed with PE and additionally include any pregnant or postpartum woman diagnosed with DVT at the participating hospitals. Inclusion of women with diagnosed DVT is planned as an efficient way of increasing the number in the cohort with VTE. There are good pathophysiological reasons for expecting candidate biomarkers to have similar sensitivity in DVT and PE, and studies of D-dimer in the non-pregnant population have shown similar sensitivity and specificity for DVT and PE (Stein 2004). Details of the biomarker study are provided on pages 18-19.

Objective 5 will be addressed by determining recruitment rates in the prospective study of women with suspected PE and determining the prevalence of PE in this population.

**3.3 A decision-analysis model** will be developed to address objectives 6 and 7. It will estimate the costs incurred and the expected outcomes from thromboembolism, bleeding and radiation exposure if a hypothetical cohort of pregnant or postpartum women were investigated for suspected PE using different strategies with a range of sensitivities and specificities, varying from no testing/treatment to imaging for all. Diagnostic accuracy will be estimated from the case-control study and other parameters from systematic literature reviews. Clinical outcomes will be modelled to estimate the costs and quality-adjusted life years (QALY) accrued by each strategy. From these data, a fully incremental cost-effectiveness analysis will be undertaken. We will estimate the value of information associated with further prospective research. Our research will identify those uncertain parameters that have the most influence on the conclusion and will identify whether any research to narrow the uncertainty in any of these parameters would be deemed cost-effective.

# 4. Selection and withdrawal of participants

**Inclusion Criteria- Diagnosed PE (Cases)**
We will identify and collect data from all pregnant and postpartum* women diagnosed with PE, defined as either
(1) PE confirmed using imaging (angiography, CT, magnetic resonance imaging or ventilation–perfusion scan showing a high probability of PE),
(2) PE confirmed at surgery or post-mortem
(3) a clinical diagnosis of PE who received a course of anticoagulation therapy for more than one week.

*The postpartum period is defined as women within 6 weeks (42 days) of the end of a pregnancy beyond the first trimester

**Exclusion criteria-- Diagnosed PE (Cases)**

(1) Women with PE identified on asymptomatic screening.

**Inclusion Criteria- Suspected PE (Controls)**

(1) Any pregnant or postpartum* woman who requires diagnostic imaging for suspected PE (as outlined above, but also including lower limb venous imaging) will be eligible for inclusion.

*The postpartum period is defined as women within 6 weeks (42 days) of the end of a pregnancy beyond the first trimester

**Exclusion criteria-- Suspected PE (Controls)**

(1) Women who need life support upon presentation to hospital (including chest compressions and assisted ventilation)
(2) Women who have been diagnosed with PE earlier in the current pregnancy and are currently receiving treatment
(3) Women who are unable or unwilling to provide informed consent.
(4) Aged <16 years

**Inclusion Criteria- Diagnosed DVT**

(1) Pregnant, or post-partum (defined as within 6 weeks of the end of a pregnancy beyond the first trimester) with a diagnosis of DVT confirmed by imaging (Ultrasound or venography)

**Exclusion criteria- Diagnosed DVT**

(1) Women with suspected PE (who should be included as suspected PE)
(2) Women who have been diagnosed with PE or DVT earlier in the current pregnancy and are currently receiving treatment
(3) Women who are unable or unwilling to provide informed consent
(4) Aged <16 years

**Sampling and Informed Consent**

**Diagnosed PE:** The sampling method has been successfully used in a previous study (Knight 2008). Nominated clinicians in each consultant-led maternity unit in the UK will be sent a card each month and asked to report all cases of antenatal or postnatal PE, thus covering the entire cohort of UK births. To ensure all cases are identified, we will independently contact all radiology departments and ask them to report any cases of PE in pregnant women, providing only their year of birth and date of diagnosis. If a case is identified which has not been reported through UKOSS, the relevant UKOSS reporting clinician will be contacted and asked to complete a data collection form. In addition, ascertainment of any maternal deaths from PE occurring during the study period will be checked through MBRRACE-UK, the collaboration responsible for the UK Confidential Enquiries into Maternal Death. Where a case is identified, the UKOSS clinician will be contacted and asked to complete a data collection form if appropriate.

It will not be practicable to obtain consent for data collection from individual women, as this would prevent the achievement of the primary objective of the study, namely to collect information on all confirmed cases of PE in pregnancy in the UK. The National

Information Governance Board (NIGB) Confidentiality Advisory Group considers that organisations seeking to use NHS information for research purposes without consent should seek anonymised or pseudonymised data only and not any personally identifiable information. Accordingly, names, addresses, postcodes, dates of birth, NHS or hospital numbers will not be collected in the UKOSS research platform. Women with diagnosed PE will be identified by a member of the clinical care team who will extract anonymised data from the hospital records. Collection of anonymised data in this way in the absence of consent is unlikely to cause significant harm. This UKOSS methodology has received the approval of the London Multi−centre Research Ethics Committee (study reference 04/MRE02/45).

**Suspected PE:** Clinical staff in the participating hospitals will be asked to prospectively identify any pregnant or post-partum women who require diagnostic imaging for suspected PE or who are in hospital after having received diagnostic imaging for suspected PE. They will provide women with information about the study and then contact the study research nurse, where possible. Research nurses, and appropriately trained clinicians who have completed Good Clinical Practice (GCP) study specific training, and are named in the delegation log will check inclusion criteria and seek informed consent to participate. Participants will be given a patient information sheet to read and approximately one hour to consider whether to take part in the study.

**Diagnosed DVT:** Clinical staff in the participating hospitals will be asked to prospectively identify any pregnant or postpartum woman with diagnosed DVT confirmed by imaging, but without suspected PE (who should be recruited as suspected PE). They will provide women with information about the study and then contact the study research nurse, where possible. Research nurses, and appropriately trained clinicians who have completed Good Clinical Practice (GCP) study specific training, and are named in the delegation log, will check inclusion criteria and seek informed consent to participate. Participants will be given a patient information sheet to read and approximately one hour to consider whether to take part in the study.

**Multiple presentations:** At participating hospitals women will not be recruited to the study more than once with the exception of women included in the Diagnosed DVT group who may re-present as a Suspected PE. These women will be identified and approached in accordance with the Suspected PE group, and will be required to provide the blood sample, regardless of whether a previous sample has been obtained when included in the Diagnosed DVT group.

Women recruited to Suspected PE who have a PE will also be reported by the UKOSS reporting clinician to UKOSS, in these circumstances multiple presentation will be handled in the analysis (p25).

Women who have previously had data collected anonymously in the Non- Recruited will be screened for eligibility to the Suspected PE and Diagnosed DVT group if they re-present.

**Withdrawal criteria**

The only withdrawal criteria are patient request for withdrawal from the study.

# 5. Assessments and procedures

## 5.1 Data Collection Procedure

### 5.1.1 Diagnosed PE
Clinicians who report a case will be asked to complete a data collection form detailing potential predictor variables, diagnostic test results, management and outcomes. Up to five reminders will be sent if completed forms are not returned. All data requested will be anonymous. On receipt of data collection forms, cases will be checked to confirm that they meet the case definition. Duplicate reports will be identified by comparing the woman's year of birth, hospital and expected date of delivery.

Collection of data on cases in this way means we are not able to alter hospital diagnostic/testing practice. Thus, to help ensure maximal information is available on diagnostic tests such as D-dimers, the information provided to UKOSS clinicians in advance of the study will highlight the relevant sections of RCOG and ESC guidance about diagnostic testing. This current guidance suggests that D-dimer testing is helpful to exclude PE, although not helpful as a marker of positivity. We will, in addition, provide staff with information about the other biomarkers of interest, and ask them to record the results of these tests if they are undertaken as part of hospital standard practice. We will monitor the completeness of data provision on diagnostic testing throughout the data collection period.

### 5.1.2 Suspected PE
The research nurse or an appropriate trained clinician will complete a data collection form incorporating standard clinical assessment. Participants will undergo diagnostic imaging according to local protocols. At 30 days after recruitment the research nurse will review hospital records and record details of any adverse events and the results of diagnostic investigations for PE. All participants, except those who have died or withdrawn from the study, will be sent a questionnaire by mail or email, or administered over the telephone, to record any additional adverse events, health care received and health utility on the EQ5D.

Where incomplete or indeterminate data impacts the ability of researchers to rule out a PE and additional adverse events, the clinical team at the participating site will contact the patient's GP on behalf of the study to obtain further data from the 30 days immediately post consent related to Suspected PE.   A data collection form will be posted to the GP for completion with a photocopy of the participant consent form and participant information sheet.

### 5.1.3 Non-recruited Suspected PE

As we recognise the difficulty in recruiting in an emergency setting, we will collect baseline non-identifiable data from the case notes of those women who were eligible but were not asked to participate in the study to  see how representative the sample of recruited women are.

### 5.1.4 Diagnosed DVT

The research nurse or an appropriate trained clinician will complete a data collection form incorporating standard clinical assessment.

### 5.1.5 Lost to follow up procedures

Participants will receive up to 3 reminders to complete the 30-day questionnaire. One of the two reminders will if possible use an alternative method of contact (e.g. phone if no response to mail).

### 5.1.6 Data collection windows

The data collection windows for the 30-day questionnaire are between and inclusive of day 23 and day 60.

Blood samples are to be taken prior to hospital discharge.

### 5.1.7 Adverse events

Adverse events are being collected in the study to input into the decision model. As this is a non-interventional study there are no safety reporting requirements.

Research nurses, and clinicians should remain vigilant to possible adverse events as result of the research processes and data collection, this may involve issues from taking an additional blood sample, issues with the venepuncture process, or delays to receiving standard care. Any possible adverse event should be recorded on the adverse event form and reported in accordance with the CTRU SOP (PM004)

### 5.1.8 Protocol Non-compliance

Protocol non-compliances will be reported as per the Sheffield CTRU SOP: and the process will be agreed with the Sponsor.

**Table 3: Data collection**

| | Where | Completed by | Format | | When | Which element (s) of the study relevant for | Purpose/Data collected |
|---|---|---|---|---|---|---|---|
| **FORMS AND OUTCOME MEASURES** | | | Paper | Electronic | | | |
| **Retrospective study: PE cases** | | | | | | | |
| UKOSS card | ED, maternity unit or medical admissions unit | UKOSS nominated clinician | x | | Sent once a month throughout study and completed when a new PE case identified | Case control study | To identify cases of PE retrospectively to enable more detailed data collection |
| Case report form | ED, maternity unit or medical admissions unit | UKOSS nominated clinician | x | | Sent in response to the UKOSS nominated clinician indicating that a PE case has been seen | Case control study, decision analytic model | To collect potential predictor variables, diagnostic test results, management and outcomes |
| **Prospective study: Suspected cases of PE (controls)** | | | | | | | |
| Eligibility criteria form | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At time of recruitment conversations (face-to-face) | Case control study | To determine eligibility for case control study |
| Informed consent | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At time of recruitment conversations (face-to-face) | Case control study | To ensure compliance with the study protocol and GCP |
| Case report form-prospective study (suspected cases of PE/controls) [Includes data collection for biomarker study (~5 PE cases identified by the prospective study, ~245 suspected PE but negative diagnostic testing and 20 DVT cases)] | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At recruitment/Baseline and at 30 days | Case control study, biomarker study, decision analytic model. | To record details of standard clinical assessment at baseline. To record details of any adverse events and the results of diagnostic investigations for PE. To evaluate potential alternative |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | biomarkers and undertake more detailed analysis of D-dimer |
| Questionnaire to record any additional adverse events, health care received and health utility on the EQ5D. | Participant's home | Participant | x | x | 30 days after baseline | Decision analytic model | To provide EQ-5D data and an estimate of health care resource use and additional adverse events. |
| Data collection form | Primary Care | General Practitioner | x | | Sent after a non-response to 30 day follow up questionnaire. | Case control study, biomarker study, decision analytic model | Record details of any adverse events, any subsequent Thromboembolic events, and additional diagnostic investigations for PE or therapeutic anticoagulation.occurring in the 30 days since consent. |
| *Feasibility outcomes* | | | | | | | |
| Number and characteristics of eligible patients approached: *screening form* | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At time of recruitment conversations | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |
| Reasons for ineligibility: *screening form* | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | X | | At time of recruitment conversations | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |
| Reasons for refused consent: *screening form* | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At time of recruitment conversations | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |
| Reasons for attrition: *withdrawal form* | ED, maternity unit or medical admissions unit | Clinical staff and Research nurse | x | | At point of study withdrawal | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |
| Participant attrition rate: | CTRU | Researcher | | x | At report writing stage | Prospective cohort feasibility | To inform feasibility of a prospective cohort |

| | | | | | | | study |
|---|---|---|---|---|---|---|---|
| Number of missing values/incomplete cases | CTRU | Researcher | | x | At report writing stage | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |
| Feasibility of recruiting participating centres | CTRU | Researcher | | x | At report writing stage | Prospective cohort feasibility | To inform feasibility of a prospective cohort study |

ED= emergency department; CTRU=clinical trials research unit

**5.2 Biomarker study**

The case-control study will allow us to evaluate routinely recorded clinical variables, including those constituting existing clinical prediction rules, and current diagnostic tests, such as D-dimer. However, we also plan to evaluate potential alternative biomarkers and undertake more detailed analysis of D-dimer to determine whether a pregnancy-specific threshold could optimise specificity without compromising sensitivity. In particular we will look at the performance of one of the most commonly used D-dimer assays in the UK (Innovance) in the summer of 2016, so that our results have applicability to current practice. Patient consent is required to take additional blood samples so the biomarker study will only include women with suspected PE recruited to the prospective study and will not include women with diagnosed PE identified through UKOSS. Since only a small number (~5) will actually have PE, we will augment the sample with pregnant or postpartum women who have DVT diagnosed during the recruitment period at the 8 participating hospitals, thus including all women with diagnosed VTE. There are good pathophysiological reasons for expecting that biomarkers will have the same sensitivity in PE and DVT and empirical studies of D-dimer have shown similar sensitivity in DVT and PE (Stein 2004).

Since the grant application for DiPEP was submitted there has been growing interest in differing measures of right ventricular strain as a consequence of pulmonary embolism. The "rising star" is MRproANP, which in comparative studies arguably may be preferable to use, as it has sensitivity and specificity possibly greater than our standards, BNP and troponin. Its use has not been assessed in pregnancy, so this study would be a useful validation of normal ranges as well as assessing its utility in those with pulmonary embolism.

Pregnant or postpartum women with suspected PE recruited to the prospective study will be asked to provide an additional blood sample when blood is taken for routine clinical care.  If it is not possible to take the additional sample at the same time as blood sampling for routine care the patient will be  asked to provide an additional blood sample, which may require the patient to undergo an additional venepuncture procedure. In addition, we will recruit any women with a DVT diagnosis confirmed by imaging (ultrasound, magnetic resonance, CT or contrast venography) who is willing to provide an additional blood sample. The incidence of DVT in pregnancy and postpartum is around 4 times that of PE (Kane 2013) so we anticipate recruiting around 20 women with DVT. Thus the sample for the biomarker sub-study will include 245 women with suspected PE but negative diagnostic testing, 5 women with diagnosed PE and 20 women with diagnosed DVT (i.e. 25 with VTE).

Blood samples will be stored and transported for analysis at Guys and St Thomas's (GSTT) Hospital. Analysis will involve (1) comparison of biomarker levels between women with and without thromboembolism, (2) construction of receiving operator characteristic (ROC) curves and calculation of the area under ROC curve, and (3) exploration of the impact of using a pregnancy-specific threshold upon the ROC analysis.

We plan to test the following biomarkers (see Table 4), along with any potential new biomarkers that become available during the project

**Table 4: Biomarkers to be tested**

| Biomarker | Description |
| --- | --- |
| D-Dimers (ELISA) | A fibrin degradation product - a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. Measured by enzyme-linked immunoassay |

| | |
|---|---|
| | (ELISA) and a highly sensitive assay. |
| D-dimers (Innovance) | As above, but near patient testing and fast turn around time allows for day- to day use. This is a point of care test that is used by many routine laboratories in the UK in 2016. |
| Plasmin-antiplasmin assay (PAP) | An ELISA assay that measures the level of plasmin-antiplasmin complexes and thus is a very sensitive assay of plasmin activation. |
| Prothrombin fragment 1+2 (PF 1 +2) | A small molecule cleaved from prothrombin when thrombin is generated. It is thus a sensitive marker of thrombin generation i.e. coagulation turnover. It is an ELISA assay |
| Thrombin Generation | Thrombin generation can be measured dynamically using the Endogenous Thrombin Potential [ETP], a term introduced by Hemker in 1986 that refers to the total amount of thrombin generated during the test. Commonly measured variables when analysing thrombin generation include the Lag Time, the Time to Peak Thrombin Generation, the Endogenous Thrombin Potential [ETP] - the area under the curve. |
| Prothrombin time (PT) | A routine measure of the extrinsic pathway of coagulation, used to determine the clotting tendency of blood. |
| Activated partial thromboplastin time (APTT) | A routine measure of the intrinsic and common coagulation pathways, used to detect abnormalities in blood clotting. |
| Clauss Fibrinogen | A functional measure of fibrinogen |
| Soluble Tissue Factor (sTF) | A marker of tissue factor activation - when tissue factor is upregulated part of the molecule enters the systemic circulation. |
| Troponin I | Part of the troponin complex in cardiac muscle tissue, used to detect myocardial damage resulting from myocardial ischaemia or noncardiac causes such as PE. |
| B-type natriuretic peptide | A polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells, used to measure heart strain resulting from primary heart disease or noncardiac causes such as PE. |
| C- Reactive Protein (CRP) | CRP is an acute-phase protein, the levels of which rise in response to inflammation. Elevation of CRP has been shown to be associated with a diagnosis of PE. |
| MRproAMP | Since the grant application for DiPEP was submitted there has been growing interest in differing measures of right ventricular strain as a consequence of pulmonary embolism. The "rising star" is MRproANP, which in comparative studies arguably may be preferable to use, as it has sensitivity and specificity possibly greater than our standards, BNP and troponin. Its use has not been assessed in pregnancy, so this study would be a useful validation of normal ranges as well as assessing its utility in those with pulmonary embolism. |

**5.3 Decision-analysis modelling**

Decision-analysis modelling will be used to estimate costs incurred and expected outcomes from thromboembolism, bleeding and radiation exposure if a hypothetical cohort of pregnant or postpartum women were investigated for suspected PE using different strategies. These will include a no imaging strategy (i.e. no treatment), imaging for all, and a range of strategies with varying sensitivity and specificity in which women are selected for imaging on the basis of clinical characteristics, a clinical prediction rule or biomarker measurement. The sensitivity and specificity of these strategies will be estimated using our primary data. Sensitivities of strategies based on clinical predictors will be estimated from the ~150 cases with diagnosed PE. Sensitivities of biomarker strategies will be estimated from the ~25 women with PE or DVT included in the biomarker study. Specificities of all strategies will be estimated from the ~245 women with suspected PE who have negative diagnostic imaging.

Each diagnostic strategy will be applied to the hypothetical cohort to estimate the number of true and false positives and negatives based upon our estimates of sensitivity and specificity. We will assume that true and false positives undergo imaging while true and false negatives are discharged without treatment. Estimates of the diagnostic accuracy of imaging (NICE, 2012) will be used to determine whether imaging results in appropriate treatment of PE or inappropriate treatment of women without PE. We will use methods developed in our evidence synthesis of diagnostic testing for DVT (Goodacre 2006, Bates 2012) to estimate the effect of treatment for PE and existing meta-analysis to estimate risks of recurrent fatal and non-fatal PE with anticoagulation, and risks of haemorrhage with anticoagulation (Carrier 2010, Linkins 1998, Douketis 2003).

Outcomes will be modelled to estimate the quality-adjusted life years (QALYs) accrued by each strategy. Existing data sources and our previous evidence synthesis projects (Goodacre 2006) will be used to estimate QALYs after PE and complications of treatment, and estimate a QALY loss for diagnostic imaging based on the risk of radiation-related malignancy. Costs for initial hospital assessment, diagnostic testing, treatment of PE and treatment of complications will be estimated using NHS reference costs. The incremental cost per QALY gained by each strategy compared to the next most effective alternative on the efficiency frontier will determine the adoption strategy at current NICE thresholds. The precise modelling methodology will be determined as the model is developed in the project. This decision will be made in conjunction with clinical experts and having assessed the available data. The research team are highly familiar with cohort Markov models and decision trees, and have published using more advanced methods such as individual patient modelling (Stevenson 2005 ), discrete event simulation (Stevenson 2010 a), area under the curve analyses (Stevenson 2010b) and meta-modelling (Stevenson 2004 ).

We will undertake sensitivity analysis, guided by input from an expert clinical group, to test key assumptions in the model, such as the assumed sensitivity and specificity of diagnostic imaging, the effect of treating PE (especially subsegmental PE), the effect of using CTPA or VQ scanning as the imaging method, and inaccuracy and imprecision in estimates of strategy diagnostic accuracy.

We will specifically undertake a sensitivity analysis to explore the effect of any potential design-related bias upon our estimates of diagnostic sensitivity. Lijmer *et al* (1999) estimated the effect of design-related bias in diagnostic accuracy studies. Use of a case-control design appears to overestimate the diagnostic odds ratio compared to a cohort design, although this may be more relevant to studies that use a control group from the normal population rather than symptomatic controls presenting with suspected

disease (as with our primary data). Nevertheless, we will use this estimate to adjust our estimates of diagnostic sensitivity to explore the potential impact of design-related bias.

Biomarker strategies will be tested using data from the biomarker study, although this analysis will inevitably be limited by the data available. Biomarkers will be selected for analysis if accuracy data suggest diagnostic value (i.e. a c-statistic significantly better than 0.5 and at least comparable to D-dimer). We will model the cost-effectiveness of each biomarker (compared to no imaging, imaging for all and imaging based on clinical predictors) at varying thresholds for positivity to estimate the optimal threshold. Sensitivity analyses will be used to explore the potential impact of uncertainty in estimates of biomarker diagnostic sensitivity, in terms of imprecision (due to the small number with VTE in the primary data), inaccuracy (due to the need to extrapolate data from VTE to those with PE) and "statistical shrinkage" (due to the use of an unvalidated data-derived threshold for positivity).

Value of information analyses will be conducted to determine the overall gain associated with: removing all uncertainty from the decision problem (Expected Value of Perfect Information); removing all uncertainty from a subset of parameters (Expected Value of Partial Perfect Information); and if these values are sufficiently large, the expected value of conducting future research assuming finite sized trials (Expected Value of Sample Information). The exact focus of such analyses would be determined during the research but candidate studies would include a prospective cohort study and the collection of further evidence to validate the adoption decision advocated by current evidence.

We will specifically use value of information analysis to explore the value of undertaking a prospective study to obtain more accurate, precise and prospectively validated estimates of diagnostic sensitivity for a clinical prediction rule or biomarker.

# 6. Statistics

**Sample size**
Data will be collected from 150 UKOSS cases with diagnosed PE and up to 325 pregnant or postpartum women with suspected PE, resulting in about 156 cases with PE and 321 controls without, assuming prevalence of PE is 2% in those with suspected PE. Potential attrition in the primary outcome data of up to 25% in the suspected PE group will allow for a sample size of 250 women with complete Suspected PE data and achieve an estimation of sensitivity or specificity of 90% with a standard error of about 2.5% and 2.0% respectively.

If we assume that the ratio of cases to controls is about 0.4, then this sample size is sufficient to identify an odds ratio of a clinical predictor of about 2, with 90% power and 5% two sided significance (Machin 2009).

**Data Analysis**

Women with PE who did not present with suspected PE prior to diagnosis, i.e. those who need life support upon presentation to hospital (including chest compressions and ventilator support) will be excluded from primary and secondary analyses, but their data used to estimate key parameters, such as incidence of PE in pregnancy and postpartum.

Two independent assessors, blind to clinical predictors and blood results, will classify participants as having PE using diagnostic imaging results, details of adverse events and details of treatments given. Disagreements will be resolved through adjudication by a third assessor. Women with a clinical diagnosis of PE based on imaging evidence of DVT will be analysed as cases. Women with a purely clinical diagnosis of PE (i.e. without any imaging evidence of DVT or PE) will be excluded from primary analysis but included as cases in secondary analysis. Women with clinically ruled out PE (i.e. suspected PE without diagnostic imaging for PE) will be excluded from the primary analysis but included as controls in secondary analysis.

Women with multiple presentations i.e. classified as having a PE in the Suspected PE group and also identified through UKOSS, will be cross referenced using the date of the PE and the woman's year of birth to ensure that case is only used once in the analysis. Similarly, for the biomarker study, women collected as a Diagnosed DVT and then also included as a Suspected PE will also cross referenced and their blood samples will be highlighted as being from the same individual.

Sensitivity, specificity, likelihood ratios and/or c-statistics will be estimated with a 95% confidence interval for clinical predictors, biomarkers and existing prediction rules (Wells, Geneva and PERC) using data from cases and controls. Chi-square or Fisher's Exact tests will be used to test the association between PE diagnosis and each clinical variables, D-dimer (dichotomised at the standard threshold) and prediction rule. Multivariate analysis will then be used to identify which variables are independent predictors of PE. If the multivariate model suggests that a new combination of variables or a modified rule could outperform existing rules we will develop a new rule from the model variables or modify an existing rule with the aim of achieving the highest specificity at which sensitivity of at least 95% is maintained. The multivariate model will be validated internally using cross-validation, i.e. the data will be split into a training and validation set at random, in the ratio 2:1 and the model fit to the training and tested in the validation test. In addition we will use bootstrapping to validate the model (Royston 2009).

Secondary analyses will explore (a) whether the findings differ between pregnant and postpartum women, and (b) whether findings are sensitive to the inclusion of women with clinically diagnosed PE in the reference standard definition. An additional secondary analysis will test the performance of a clinical decision rule developed through expert consensus. Standard Delphi and Nominal Group methodology will be used with panel membership including obstetric, emergency medicine, haematology, and radiology expertise (Dalkey 1972, Delbecq and Van de Ven 1971). The sensitivity and specificity of the resulting CDR for identifying diagnosed PE will then be determined in the DiPEP cohort.

Further details will be provided in a separate statistical analysis plan.

# 7. Study supervision

A Steering Committee will be appointed to provide independent oversight. It will consist of SG, the project manager, two patient/public representatives (Franchesca Cullinane and Shan Bennett) and four independent experts, one of whom will chair the committee.

The study will be managed by a full-time project manager based in the Sheffield CTRU. The CTRU will also provide data management, statistical and health economic support. A Project Management Group consisting of the co-applicants and appointed research staff will undertake day to day management of the study and will meet at least quarterly.

The study Sponsor will be Sheffield Teaching Hospitals NHS Foundation Trust and SG will take overall responsibility for the study.

There will be no Data Monitoring and Ethics Committee (DMEC) required for this study. A data management and monitoring plan will be devised in accordance with the Sheffield CTRU SOP (DM009)

Subcontracts will be drawn up between the University of Sheffield and other participating institutions. Marian Knight from the National Perinatal Epidemiology Unit will be responsible for the UKOSS research platform to identify cases of diagnosed PE. Beverley Hunt from Guy's and St Thomas's Hospital will be responsible for the biomarker analysis.

# 8. Plan of investigation and timetable

The project will take 30 months to complete and will involve three phases:
Phase 1 will take six months (1/10/14-31/3/15) and involve obtaining ethics and R&D approval, setting up the project across participating sites, updating the literature review and finalising data collection.
Phase 2 will take 18 months (1/4/15-30/9/16) and involve primary data collection for cases (UKOSS, all UK hospitals commencing 1/4/15) and controls (11 hospitals, staggered start from 1/4/15 to 30/9/15), and development of the decision-analysis model.
Phase 3 will take six months (1/10/16-31/3/17) and involve follow-up, analysis, incorporation of primary data into the model and writing-up.

Progress reports will be submitted 6-monthly:

1.  31/3/15: Details of approvals, finalised protocol and data collection
2.  30/9/15: Identification of diagnosed PE started from the UKOSS research platform (target=50) and recruitment of suspected PE started at all eleven hospitals (target=50)
3.  31/3/16: Progress on identification of diagnosed PE (target=100) and recruitment of suspected PE (target=150)
4.  30/9/16: Progress on identification of diagnosed PE (target=150) and recruitment of suspected PE (target=325)

# 9. Data handling and record keeping

Participant confidentiality will be respected at all times during the DiPEP project. Data will be collected and handled in line with CTRU Standard Operating Procedures and in accordance with NHS Trust policies at Sheffield Teaching Hospitals NHS Foundation

Trust and at each participating site. This will ensure systems are in place to protect confidentiality of participants and the systems are secure.

The UKOSS research platform will not collect names, addresses, postcodes, dates of birth, NHS or hospital numbers. Women with diagnosed PE will be identified by a member of the clinical care team who will extract anonymised data from the hospital records. Data will be recorded on a case report form with a unique study number but no personal details. For UKOSS cases, the case report form will be mailed to UKOSS at the National Perinatal Epidemiology Unit at the University of Oxford. Data will be entered onto a secure password protected electronic database within UKOSS. The database will then be emailed to Sheffield CTRU with the password mailed separately. The paper case report forms will be destroyed when data entry and data checking is complete.

For women with suspected PE, data will be entered onto a secure online database by a clinical research nurse employed by the hospital. A separate database held within the hospital by the principal investigator or research nurse will link the unique study number to the patient's hospital number to allow audit, avoid duplication and avoid repeated requests to participate resulting from multiple admissions. Patient name, telephone number, email and/or address will be entered onto the secure online database for women consenting to questionnaire follow-up. These details will be recorded on the case report form but will be blacked out on the paper form when they are entered onto the online database.

Bloods samples from women with suspected PE will be will be identified by unique study identifier only. This will allow us to link to the patient records for purposes of audit and monitoring. The researchers analysing the blood samples at GSTT will not have access to personal details and blood results will not be made available to anyone associated with the patient or involved in their care.

All consent forms, CRFs, questionnaires will be kept in a locked filing cabinet in a secured area and will be destroyed at least 5 years after study completion. The consent forms will be kept in a separate place to the CRFs and questionnaires so that none of the data will be identifiable.

# 10. Data access and quality assurance

For the UKOSS research platform, the security of all data will be maintained by storage on a secure University network, accessible only by the key researchers and responsible members of the University of Oxford who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after review by the UK Obstetric Surveillance System Steering Committee and further reference to a Research Ethics Committee.

For the suspected PE part of this study, the study manager, research assistant and data managers based at Sheffield CTRU will have access to the anonymised data on the database through the use of usernames and encrypted passwords. Select CTRU staff will have access to personal data including names, addresses, phone numbers and email addresses in order to undertake the questionnaire follow-up. In addition to this, access to hard copies of the CRF and questionnaire data will be required for study monitoring and audit purposes. A study monitoring plan will be devised in accordance

with the Sheffield CTRU SOPs on Trial Monitoring (QU001) and Data management and monitoring plan (DM009).

The study database resides on Sheffield CTRU's in house data management system. The system uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

# 11. Publication

We have strong links with guideline development groups and our previous research has influenced a number of national and international guidelines. Our previous HTA-funded evidence synthesis on diagnostic testing for DVT (Goodacre 2006) formed the basis of NICE guidance (NICE 2012) and American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for DVT diagnosis (Bates 2012).

Indiscriminate use of diagnostic imaging for women with suspected PE in pregnancy is unsurprising given the lack of evidence that any clinical predictor, rule or biomarker can rule-out PE in this patient group. This study will be the first to provide reasonably precise estimates of the sensitivity of clinical assessments. If it shows that a clinical predictor, rule or biomarker can rule-out PE then this will for the first time provide clinicians and guideline-developers evidence that a simple diagnostic strategy can safely reduce the use of imaging and associated health care costs.

It is entirely possible that this study will show that an existing clinical prediction rule and/or the use of D-dimer at an appropriate threshold can rule-out PE and achieve sufficient specificity to allow a substantial proportion of women to avoid imaging. If not, our data will allow us to modify existing rules or develop a new rule with greater sensitivity and specificity. Any new rule would need validation in a new study. We will determine whether a prospective cohort study is feasible, and whether such a study would represent value for money.

Estimation of biomarker levels in women with suspected PE but negative testing will help clinicians to interpret blood test data and identify which biomarkers may be diagnostically useful in pregnancy. Normal ranges for biomarkers are currently based on non-pregnant populations and even when they have been measured in pregnant patients these are not patients with symptoms suggestive of PE.

Decision-analysis modelling will provide estimates of the relative benefits, harms and costs of testing for suspected PE in pregnant and postpartum women with varying risk of PE. These findings will help clinicians to make individualised decisions about the use of imaging and potentially allow informed patient involvement in decision-making. We will specifically identify the threshold of risk of PE at which the benefits of imaging outweigh the harms and the threshold at which the benefit justifies the costs.

We will disseminate our findings in the following ways:

1. We will send a scientific summary of our findings along with access to the full report to organisations responsible for producing guidelines for the investigation of suspected PE in pregnant and postpartum women and professional or academic bodies with an interest in this area, including the NICE, the Royal College of Obstetricians and Gynaecologists, the College of Emergency Medicine, the Royal College of Radiologists, the British Society for Haematology, the American Thoracic Society and the European Society for Cardiology.
2. We will disseminate plain language summaries of our findings to patient and public representative organisations.
3. We will produce a plain language information leaflet for women explaining the risks and benefits of testing for suspected PE in pregnancy and postpartum, and disseminate this, along with the summary of our findings, to organisations responsible for producing guidelines and organisations responsible for providing care for women with suspected PE in pregnancy and postpartum.
4. Scientific papers produced in this project will be submitted to high profile journals that provide open access and are widely read by those responsible for diagnostic investigation of women with suspected PE in pregnancy and postpartum.
5. Findings will be submitted for presentation at relevant conferences. We will also develop supporting material to assist dissemination at professional meetings.
6. We will publicise key scientific outputs by issuing press releases to established media contacts, making research team members available for interview, and using our website, blog, facebook page and twitter feed.

# 12. Finance

The trial has been financed by the HTA and details have been drawn up in a separate agreement.

# 13. Ethics approval

The trial will be submitted to a Local Research Ethics Committee (LREC) through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information sheet, consent forms, CRFs and questionnaires will be sent to the CTRU before initiation of the study and patient recruitment.

# 14. Indemnity / Compensation / Insurance

This is an NHS sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study. The University of Oxford maintains public and private liability insurance in this respect.

## 15. Patient and Public Involvement

We are involving patient and public representatives in developing this proposal and undertaking the research with the aim of ensuring that study procedures are acceptable to participants, that outputs are comprehensible to patients and the public, and that patient and public perspectives are central to informing our understanding of the benefits, risks and costs of investigating suspected PE in pregnancy.

Members of our team have strong links with patient and public representative groups. BH is co-founder and Medical Director of Thrombosis UK, which campaigns to raise awareness of thrombosis (http://www.thrombosis-charity.org.uk). SG has strong links with the Sheffield Emergency Care Forum (SECF), a public and patient representative group involved in emergency care research (http://secf.org.uk). Representatives of both groups have reviewed the outline proposal, are supportive of the research and are willing to assist with development of the proposal and delivering the research. Tracy Lamb and Franchesca Cullinane from Thrombosis UK and Shan Bennett from SECF have agreed to join the study Steering Committee. We will specifically ask patient and public representatives to review plain language descriptions of th
e diagnostic strategies investigated in the decision-analysis model, along with their modelled outcomes, and comment on the acceptability of strategies to patients.

Lay representatives from the UKOSS Steering Committee have been consulted about the development and acceptability of the UKOSS protocol, data collection form, information and other materials.

## 16. Expertise of the Research Team

Steve Goodacre is an NIHR Senior Investigator and emergency medicine researcher who has led many successful NIHR-funded primary and secondary research projects.

Fiona Lecky was co PI on the THREAD study which prospectively recruited 800 patients with suspected VTE and leads the local Injuries and Emergencies specialty group.

Catherine Nelson-Piercy is a consultant physician and manages women with VTE in pregnancy. She has published extensively on VTE in pregnancy and is the lead developer of the RCOG Guideline on Thromboprophylaxis in pregnancy.

Beverley Hunt co-founded the BSH Obstetric Haematology group and co-edited the standard textbook on this topic. She has been actively researching thrombosis in pregnancy for 20 years. She sat on the NICE GDG for managing (CG144) and preventing (CG92) VTE.

Steve Thomas is an experienced researcher and vascular radiologist.

Matt Stevenson is an experienced mathematical modeller and a NICE committee member who has led numerous HTA-funded evidence-synthesis projects. He will ensure that the modelling is undertaken to a high standard.

Judith Cohen is an experienced trial manager and Assistant Director of the Sheffield CTRU which is currently involved in the management of 10 HTA-funded studies. She

has experience of HTA-funded research in the emergency setting having been trial manager for the successfully completed 3Mg trial.

Mike Campbell is a medical statistician with experience of working in diagnostic studies. He is the lead statistician of the MERIDIAN study, looking at the use of MRI in foetal brain malformations.

Marian Knight is an NIHR Research Professor in Public Health with extensive experience as a Health Services Researcher focusing on severe complications in pregnancy who leads UKOSS and the UK Confidential Enquiries into Maternal Deaths. She has led many successful NIHR-funded primary and secondary research projects. She will provide overall supervision and direction of the UKOSS data collection on cases.

Wee Shian Chan has been the primary investigator of diagnostic studies involving the diagnosis of DVT in pregnancy. She has developed clinical prediction rules & D-dimer levels appropriate for these patients. She has recently completed enrolment of a prospective study of PE in pregnancy.

# 17. References

Abele JT and Sunner P (2013) The clinical utility of a diagnostic imaging algorithm incorporating low-dose perfusion scans in the evaluation of pregnant patients with clinically suspected pulmonary embolism. Clin Nucl Med, 38, 29-32.

Balan KK et al (1997) The value of ventilation-perfusion imaging in pregnancy. Br J Radiol, 70, 338-340.

Bates SM et al (2012) Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2)(Suppl), e351S–e418S

Bourjeily G et al (2012) Outcomes of Negative Multidetector Computed Tomography with Pulmonary Angiography in Pregnant Women Suspected of Pulmonary Embolism. Lung, 190, 105–111.

Cahill AG et al (2009) Diagnosing pulmonary embolism in pregnancy using computed-tomographic angiography or ventilation-perfusion. Obstet Gynecol, 114, 124–129.

Carrier M et al (2010) Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med, 152, 578-589.

Chan WS et al (2002) Suspected pulmonary embolism in pregnancy: Clinical presentation, results of lung scanning and subsequent maternal and pediatric outcomes. Arch Intern, 162, 1170-1175.

Chan WS et al (2007) A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. Ann Intern Med, 147, 165–170.

Chan WS et al (2010) D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. J Thromb Haemost, 8, 1004–1011.

Cutts BA et al (2014) The Utility of the Wells Clinical Prediction Model and Ventilation-Perfusion Scanning for Pulmonary Embolism in Pregnancy. Blood Coagulation and Fibrinolysis, in press.

Dalkey, N. C. (1972). The Delphi method: An experimental study of group opinion. In N. C. Dalkey, D. L. Rourke, R. Lewis, & D. Snyder (Eds.). Studies in the quality of life: Delphi and decision-making (pp. 13-54). Lexington, MA: Lexington Books.
Damodaram M et al (2009) D-dimers as a screening test for venous thromboembolism in pregnancy: is it of any use? J Obstet Gynaecol, 29, 101–103.

Delbecq AL, van de Ven AH (1971) A group process model for problem identification and program planning. *Applied Behavioural Science,* 7(4): 466–91.Deutsch AB et al (2010) Assessment of the alveolar-arterial oxygen gradient as a screening test for pulmonary embolism in pregnancy. American Journal of Obstetrics & Gynecology, 203, 373-374.

Douketis JD et al (1998) Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA, 279, 458-62.

Goodacre S et al (2006). Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess, 15(10).

Hassanin IMA et al (2011) D-dimer testing versus multislice computed tomography in the diagnosis of postpartum pulmonary embolism in symptomatic high-risk women. International Journal of Gynecology and Obstetrics, 115, 200-201.

Henriksson P  et al (2013) Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. BMJ, 346, e8632.

Kane EV et al (2013) A population-based study of venous thrombosis in pregnancy in Scotland 1980–2005. Eur J Obstet Gynecol , http://dx.doi.org/10.1016/j.ejogrb.2013.03.024

Knight M et al (2008) Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG, 115, 453–461.

Kovac M et al (2010) The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol, 148, 27–30.

Leung AN et al (2011) An Official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline: Evaluation of Suspected Pulmonary Embolism In Pregnancy. Am J Respir Crit Care Med, 184, 1200–1208.

Lijmer JG et al (1999) Empirical evidence of design-related bias in studies of diagnostic tests. JAMA, 282(11), 1061-1066

Linkins L et al (2003) Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: A meta-analysis. Ann Intern Med, 139, 893-900.

Machin et al (2009) Sample size tables for clinical studies. Wiley Blackwell p41

National Institute for Health and Care Excellence (2012) NICE clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. http://guidance.nice.org.uk/CG144

Nijkeuter M et al (2013) Safety of ruling out pulmonary embolism (PE) in pregnancy by computed tomography pulmonary angiography (CTPA). International Society on Thrombosis and Haemostasis Congress, Amsterdam.

O'Connor C et al (2011) The application of a clinical risk stratification score may reduce unnecessary investigations for pulmonary embolism in pregnancy. J Matern Fetal Neonatal Med, 24, 1461-4.

Royal College of Obstetricians and Gynaecologists (2010) The acute management of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37b.

Royston P et al (2009) Prognosis and prognostic research: developing a prognostic model. BMJ, 338, b604.

Scarsbrook AF et al (2007) Perfusion scintigraphy: diagnostic utility in pregnant women with suspected pulmonary embolic disease. Eur Radiol, 17, 2554-2560.

Shahir K et al (2010) Pulmonary Embolism in Pregnancy: CT Pulmonary Angiography Versus Perfusion Scanning. AJR, 195, W214–W220.

Stein PD et al (2004) D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med, 140(8), 589-602.

Stevenson MD, Brazier JE, Calvert NW, Lloyd-Jones M, Oakley J, Kanis JA. Description of an individual patient methodology for calculating the cost-effectiveness of treatments for osteoporosis in women. Journal of Operational Research Society. 2005; 56 (2): 214-221.

Stevenson MD, Simpson EL, Rawdin AC, Papaioannou DE. A review of discrete event simulation in National Coordinating Centre for Health Technology Assessment funded work and a case study exploring the cost-effectiveness of testing for thrombophilia in patients presenting with an initial idiopathic venous thromboembolism. Journal of Simulation 2010; 4 14-23.

Stevenson MD, Scope A, Sutcliffe PA. The cost effectiveness of group cognitive behavioural therapy compared with routine primary care for women with postnatal depression in the UK. Value In Health 2010; 13(5) 580-584.

Stevenson MD, Oakley J, Chilcott JB. Gaussian process modelling in conjunction with individual patient simulation modelling. A case study describing the calculation of cost-effectiveness ratios for the treatment of osteoporosis. Med Decis Making 2004; 24 (1) 89-100.

Sultan AA et al (2013) Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England. BMJ, 347, f6099.

Torbicki A et al (2008) Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute

Pulmonary Embolism of the European Society of Cardiology (ESC). European Heart Journal, 29, 2276–2315.

Vinayakamoorthy V et al (2010) A United Kingdom based survey of clinical practice in the diagnosis of suspected pulmonary embolism. Nucl Med Commun, 31(2), 112-20.

Wiener RS et al (2013) When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ, 347, f3368.