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# The OPTICA study (Optimised Computed Tomography Pulmonary Angiography in Pregnancy Quality and Safety study): Rationale and design of a prospective trial assessing the quality and safety of an optimised CTPA protocol in pregnancy

Ciara Gillespie[a,b,*], Shane Foley[c], Michael Rowan[d], Karl Ewins[b,e], Fionnuala NiAinle[b,e], Peter MacMahon[a,b]

[a] Department of Radiology, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland and UCD School of Medicine, Belfield, Dublin 4, Ireland
[b] Irish Network for VTE Research (INViTE), Ireland
[c] Radiography & Diagnostic Imaging, School of Medicine, University College Dublin (UCD), Belfield, Dublin 4, Ireland
[d] Department of Medical Physics and Bioengineering, St James' Hospital, Dublin 8, Ireland
[e] Department of Haematology, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland and UCD School of Medicine, Dublin, Ireland

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ABSTRACT

*Background:* CTPA is the gold standard investigation for evaluating suspected pulmonary embolism (PE) in the general population however is sometimes considered second line in pregnant and post-partum patients with a normal CXR due to its higher breast dose and the increased radio-sensitivity of breast tissue during this period. Guidelines advocating for scintigraphy over CTPA, however, quote significantly higher breast doses than those achievable with optimised low dose strategies. Defining the radiation dose achievable with a specific low-dose CTPA protocol is therefore imperative. As decreasing dose is associated with increased image noise, demonstrating the image quality and validity of a negative low-dose CTPA in out-ruling PE in this population is necessary.

*Methods:* The OPTICA study is a prospective multicentre observational study aiming to validate the clinical utility and safety of an optimised low-dose CTPA protocol in pregnancy. An optimised low-dose CTPA protocol has been agreed across all study sites with equivalent CT capabilities. Pregnant women undergoing CTPA for suspected PE will be included. Independent review of CTPAs by two radiology consultants, image data analysis and 3-month patient follow up will be performed. The primary outcome is the 3-month incidence of VTE in pregnant patients in whom PE was excluded at baseline CTPA. Secondary outcomes will confirm the associated radiation dose and image quality of this protocol. The radiation dose will be calculated using the Monte Carlo method and will include maternal effective, breast and foetal doses. Image quality will be assessed objectively by measuring opacification of the main pulmonary trunk, signal-to-noise and contrast-to-noise ratios and subjectively using a grading scale and inter-reader variability of CTPA results.

*Conclusion:* The OPTICA study is the first prospective trial of a low-dose CTPA protocol in the pregnant population. It will provide high-quality evidence defining the achievable dose, image quality and safety of an optimised CTPA for this population. It will assist other institutes with similar CT capabilities in achieving comparable low doses for its patients and provide an evidence base upon which modern CTPA protocols can be appropriately compared to scintigraphy in the pregnant population.

## 1. Introduction

Pulmonary embolism (PE) is the leading cause of pregnancy-associated maternal death in developed countries [1]. The relative risk of venous thromboembolism (VTE) in pregnancy is approximately five times greater than that for non-pregnant women of similar age and increases further in the post-partum period (~10–20 fold) before returning to the non-pregnant level at 6 weeks post-partum [2]. VTE is

*Abbreviations:* CTPA, Computed tomography pulmonary angiogram; VTE, venous thromboembolism; NPV, negative predictive value

* Corresponding author at: Department of Radiology, Mater Misericordiae University Hospital, Level 2 Whitty Building, Eccles Street, Dublin 7, Ireland.
*E-mail address:* ciaragillespieMMUH@gmail.com (C. Gillespie).

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confirmed in fewer than 10% of women with suspected deep venous thrombosis (DVT) or PE [3]. Identifying which patients warrant imaging is challenging because the presenting features of PE, such as dyspnoea and lower limb swelling, overlap with those of normal pregnancy and d-dimer levels are often raised in normal pregnancy. Currently the majority of pregnant and puerperal patients presenting with features suggestive of PE are likely to progress to imaging due to a lack of validated clinical decision rules (CDRs). The eagerly anticipated validation of CDRs in this population [4,5] will soon aid in identifying those with a higher pre-test probability of PE. This will substantially advance the management of suspected PE in this population and result in an overall reduction in the numbers requiring imaging. However even after the implementation of CDRs, a significant number of patients are likely to require imaging and for those the question of the most appropriate imaging modality remains.

Current guidelines for the investigation of PE in pregnancy (Table 1) advise use of pulmonary scintigraphy if available, over CTPA, in cases with a normal baseline CXR [1–3,6]. Some guidelines, as in the case of the British Thoracic Society guidelines, offer no specific advice for the pregnant population [7]. CTPA therefore, albeit the gold standard imaging test in the non-pregnant population, is sometimes considered second line in the pregnant/post-partum population. The foetal dose, although higher for VQ than for CTPA, is considered sufficiently low in both modalities that it does not pose significant risk of foetal harm and thus has not to date significantly contributed to the debate on the most appropriate investigation for pregnancy-related PE [1,2,8]. The preference for pulmonary scintigraphy over CTPA is therefore primarily due to maternal breast radiation dose and initial reports of a higher indeterminate rate for CTPA than scintigraphy in the pregnant population [1,3,9].

CTPA protocols adapted to the altered physiology of pregnancy, however, have subsequently reduced the indeterminate rate and thereby increased the sensitivity/specificity and ultimately the reliability of CTPA in the pregnant/puerperal population. Recent studies now report similar indeterminate rates between CTPA and scintigraphy [11–12]. This has been achieved by reducing the transient interruption of contrast by unopacified blood from the IVC, through patient coaching to ensure shallow respiration during the scan and through use of a high concentration, high volume, high injection rate for the contrast bolus [13].

While CTPA is now established as a reliable test in pregnancy, with similar negative predictive value, indeterminate rates and false negative rates to scintigraphy [14,15], breast dose remains the outstanding issue

**Table 1**
Summary of recommendations and quoted radiation doses from relevant guidelines.

| Guideline | Main recommendations | Referenced dose ranges: | | |
|---|---|---|---|---|
| | | Maternal effective dose | Breast dose mGy | Foetal dose mGy |
| American Thoracic Society/Society of Thoracic Radiology, 2012 | | | | |
| An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline – evaluation of suspected PE in pregnancy. [3] | • CXR as first radiation associated test<br>• Scintigraphy if CXR normal and CTPA if CXR abnormal<br>• Advise CTPA in setting of (normal CXR with) nondiagnostic scintigraphy | CTPA: 4–18 mSv<br>VQ: 1–2.5 mSv | CTPA: 10–60<br>VQ: 0.98–1.07 | CTPA: 0.03–0.66<br>VQ: 0.32–0.74 |
| European Society of Cardiology, 2014 | | | | |
| 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism [1] | • Apply usual D-Dimer range to out-rule PE in pregnancy.<br>• Consider US lower limb if abnormal D-dimer. If US negative pursue diagnosis.<br>• Scintigraphy may be preferred over CT: Perfusion (Q) component only, if CXR normal (ventilation component not required). | – | CTPA: 10–70<br>Low dose Q (40 MBq): 0.28–0.50<br>High dose Q (200 MBq): 1.2 | CTPA: 0.24–0.66<br>Low dose Q only: 0.11–0.2<br>High dose Q only: 0.2–0.6 |
| The Society of Thrombosis and Haemostasis, 2016 | | | | |
| Diagnosis of pregnancy-associated venous thromboembolism – position paper of the working group in women's heath of the society of thrombosis and haemostasis (GTH) [2] | • Low dose Q (perfusion component) if normal CXR.<br>• CTPA if CXR abnormal or if scintigraphy is non-conclusive or unavailable.<br>• Negative D-Dimer can outrule PE with the same likelihood as it would in the normal population. (Although a negative result is less likely in later pregnancy.) No validated pregnancy related cut offs.<br>• Consider lower limb US ± echocardiography to substantiate suspicion of PE and confirm DVT prior to chest imaging | CTPA: 7–70<br>Low dose Q only: 0.2–1.2 | – | CTPA: 0.01–0.66<br>Low dose Q only 0.1–0.6 |
| Royal College of Obstetricians and Gynaecologists, 2015 | | | | |
| Thromboembolic disease in pregnancy and the puerperium: acute management. Greentop guideline no 37b. [6] | • D-dimer should not be performed<br>• Treat with LMWH until PE excluded, unless strongly contraindicated<br>• ECG and CXR should be performed<br>• Lower limb US if suspect DVT, no further testing if positive.<br>• VQ or CTPA if no signs DVT.<br>• Advise CTPA over VQ if CXR abnormal | – | CTPA: up to 20 mGy | – |
| British Thoracic Society, 2003 | | | | |
| British Thoracic Society Guidelines for the management of suspected acute pulmonary embolism. 2003 [7] | No specific advice for pregnant/post-partum population. Superceded by NICE Guideline CG144. | | | |
| NICE Guideline, 2012 | | | | |
| NICE Guideline CG144; "Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing." [10] | Does not cover pregnant/post-partum population | | | |

precluding its use as a first line investigation in suspected PE in this cohort. This is because breast tissue in pregnancy and the puerperium is considered to be more radiosensitive, with increased glandular activity in the presence of altered hormones postulated as the mechanism behind this theory [16]. Regarding dose, however, the heterogeneity of studies within the literature has led to a wide variation in reported CTPA doses. This is partly due to variations in CT technology, both between and within studies, different CT parameter settings and varying methods for quoting and calculating dose. Reported breast doses in the literature range from 10 to 70 mGy [8,17–20] with one recent survey of practice in the UK reporting a range of 2–14 mGy [11]. The maternal mean effective dose quoted in the literature ranges from 1.1 mSv–18 mSV [3,21] and studies using mathematical anthropomorphic phantoms propose foetal doses in the range of 0.01–0.6 mGy [22–24] with later gestation being associated with a higher absorbed dose.

### 1.1. Modern CT technology and protocols

By comparison our institutes CTPA foetal dose (estimated by dose to uterus), maternal mean effective dose and maternal breast dose estimated by the MonteCarlo method [25–26], are 0.04 mGy, 1.1 mSv and 3.3 mGy respectively. This is in use since 2015 in our institute, with demonstrated image quality [27] and is achieved through a combination of modern CT technology and protocol adaptations which balance dose with image quality considerations.

Advances in CT technology and computing power in the last 10–15 years have enabled the exploitation of powerful image reconstruction algorithms which overcome noise without increasing dose. Ultimately, newer generation CT technology can exploit these “iterative reconstruction” algorithms to provide CTPA images of equivalent quality (noise levels) to the older “filtered back projection” algorithms, at a much lower dose. Employing auto-modulation enabled technology further reduces dose. This feature automatically tailors the X-ray beam kV (kilovoltage or beam energy) and beam current (mAs) to the patient weight and size based on an initial pre-scan exposure called the topogram. This allows a lower beam energy or current to be employed in smaller patients, which do not require the same dose to achieve an adequate quality image. A similar process is employed during the scan when the variation in penetrability of the patient changes along the z-axis dependent on the size or density of structures encountered. This technology; iterative reconstruction algorithms and automodulation, is increasingly widespread and will become the norm as institutes update their CT scanners in the coming years.

Protocol adaptations employed to further reduce dose include use of a reduced scan range [28–29] and reduced kV settings for the contrast-monitoring component of a protocol [27]. Breast shields are not commonly employed in conjunction with modern CT mainly due to the comparable and more reproducible dose reduction achieved with low-dose CT strategies alone. However as breast dose remains critical to choice of imaging modality for this population, shields may yet play a role in optimising dose in this specific patient group.

### 1.2. Comparing modalities

The fact that significantly higher doses continue to be quoted in the more recent literature, up to 50 mSv for CTPA breast dose [30], despite the now widespread availability of modern CT technology may reflect a lack of experience with low dose optimisation techniques or a lack of confidence in the ability of low-dose protocols to maintain image quality and thereby safely diagnose or exclude PE in this patient population. The latter being of particular relevance given previous concerns regarding high indeterminate/non-diagnostic rates in this patient group.

Given the added advantages that CTPA poses over scintigraphy including its availability out of hours and capacity to provide alternative diagnoses, it is important to compare modalities appropriately. Prior retrospective CTPA studies in pregnancy have been limited by small patient numbers and long study durations which span the implementation of a number of protocols and multiple generations of CT technology. By contrast, an evaluation of the breast dose achievable with a single specified CTPA protocol is required to adequately compare these modalities.

Furthermore an optimum CTPA protocol for this population has not been fully described and there are no large scale prospective studies evaluating the safety of low-dose CTPA in the pregnant population. The OPTICA study aims to address this by describing a low-dose CTPA protocol optimised for the pregnant population and demonstrating the safety of this protocol in out-ruling PE in this population. This will provide an up-to-date analysis of the breast dose achievable with modern CT technology and an evidence base for judging the appropriateness of modern CTPA protocols in the pregnant population.

## 2. Study objective and hypothesis

### 2.1. Study design

The OPTICA study is an investigator-initiated, multicentre, prospective observational study for the safety, radiation dose and image quality of CTPA in pregnancy.

### 2.2. Overview of study

All pregnant women with suspected PE are investigated according to a diagnostic pathway reflecting current established guidelines necessitating chest X-ray, followed by Doppler ultrasound in cases with lower limb symptoms, followed by CTPA if advanced chest imaging is required. CTPA is offered first line, over scintigraphy, for all pregnant women with suspected PE in participating sites and the same CTPA protocol is agreed across all sites.

The study protocol was reviewed and approved by the ethics committee of the Mater Misericordiae University Hospital, Dublin. In each participating centre, the protocol will be reviewed by the local ethics committee or institutional review board.

Informed consent will be obtained from eligible women at the time of, or shortly after, their index CTPA. The OPTICA CTPA protocol is agreed across participating sites for use in all pregnant patients with suspected PE, regardless of participation in the OPTICA study. Consent therefore pertains to clinical follow up at 3 months and permission to access the patient's health record and subsequent imaging during follow up. Consent is obtained by the site researcher, radiographer or radiologist involved in patient care at time of CTPA.

In cases of indeterminate CTPA a second radiologist consultant review is sought, followed by MDT discussion (consultant radiologist and consultant haematologist with special interest in VTE) to review the clinical suspicion in light of the imaging findings, if required. Any patients with indeterminate studies will be reported and their subsequent investigation/management described.

A researcher will follow up patients with negative CTPA by phone interview at 3 months (see Section 2.7). Any subsequent diagnosis of VTE, is reviewed and judged by a central independent adjudication committee in order to determine incidence of VTE at 3 months. The protocol does not dictate the imaging modality to be used for recurrent suspected PE within the follow up period. This remains at the discretion of the primary team.

Image Quality: A central independent adjudication committee (CIAC), consisting of two consultant radiologists with 6 and 2 years of experience respectively, who are blinded to the initial CTPA report, will review the CTPA images to adjudicate all suspected episodes of PE (positive/negative, location within the pulmonary tree and alternative diagnoses) and provide a subjective image quality grading score for each CTPA. Inter-reader variability, the proportion of positive, negative and indeterminate CTPAs and the number of CTPAs yielding alternative diagnoses will be assessed. The mean pulmonary trunk enhancement,

**Table 2**
Inclusion and exclusion criteria of the OPTICA study.

Inclusion criteria:
1. Pregnant patients with a suspected pulmonary embolism
2. Age ≥ 18 years

Exclusion criteria
1. Age < 18 years
2. Ultrasound proof of symptomatic proximal DVT
3. Contraindication to helical CT because of allergy to intravenous iodinated contrast or renal insufficiency (creatinine clearance < 30 ml/min)
4. Treatment with full-dose therapeutic low molecular weight heparin or unfractionated heparin initiated 24 h or more prior to eligibility assessment
5. Treatment with vitamin K antagonists (coumarin derivates i.e. warfarin)
6. Unable or unwilling to consent
7. Unable to part-take in follow-up
8. Life expectancy < 3 months

signal-to-noise-ratio (SNR) and contrast-to-noise-ratio (CNR) for each CTPA will be calculated.

Radiation Dose: The maternal effective dose, breast dose and foetal dose associated with each CTPA will be calculated using the Monte Carlo Simulation method [25–26]. In a small number of patients there will be an additional skin dose measurement taken at the breast using TLDs. This will be done for a small subgroup of patients who will be offered the option of wearing breast shields during the CTPA scan.

### 2.3. Patient population and eligibility

Pregnant women with suspected PE who are over 18 years of age are eligible for the study. The inclusion and exclusion criteria are listed in Table 2.

The source population includes pregnant patients presenting to the emergency departments of participating sites directly, as well as those referred from local maternity hospitals (maternity ED, maternity hospital outpatients and inpatients) for CTPA in the participating site.

### 2.4. CTPA protocol

All enrolled patients will undergo the same CTPA protocol as described below (Table 3). All CTPAs will be performed using an iterative reconstruction capable multislice CT scanner (minimum 64slice). In the Mater Misericordiae University Hospital, Dublin, this will be a 128slice CT system (somatom Definition AS+, Siemens Healthcare, Forchheim, Germany).

The CT machine will be automatic mAs capable with automatic kV modulation enabled (CAREdose 4D and CAREkV; Siemens Healthcare). A reference tube current of 90mAs will be chosen with a pitch of 1.2 and rotation time of 0.3 s. Regarding automatic kV modulation; a topogram will be performed at 80 kV, which determines the appropriate kV and mAs of the diagnostic study (CARE kV; Siemens Healthcare.) Care kV is prevented from automatically adjusting the kV for the contrast monitoring scan, which will be set at 80 kV. A bolus tracking technique is to be used, use of a test bolus timing technique is not accepted. The scan range will be limited to; below the humeral head to just below (approximately 2 cm) the tip of the lowest hemi-diaphragm (see Fig. 1). Intravenous contrast with minimum iodine concentration of 370 mg/ml should be used, typically 60 ml of non-ionic iodinated contrast (lopamidol, Isovue 370; Bracco Diagnostics Inc., USA). An injection rate of 4–5 ml/s will be performed via the antecubital fossa using a dual headed pump injector (Swiss Medical Care, Lausanne, Switzerland) with a 20 ml saline flush. Breathing instructions are to result in a shallow inspiratory breath hold. Deep inspiratory effort is to be avoided. In a small number of patients, breast shields will also be draped over the chest wall, post topogram, for the CTPA scan.

**Table 3**
CTPA protocol parameters and settings.

| CTPA protocol parameters | |
|---|---|
| kV | AutokV – kV chosen based on topogram |
| Topogram | 80 kV |
| Bolus tracking component | 80 kV |
| mAs | 90mAs (reference tube current) |
| Pitch | 1.2 |
| Rotation time | 0.3 s |
| Scan range | Below humeral heads to 2 cm below dome of diaphragm |
| IV contrast | 60 ml of 370 mg/ml at 5 ml/s with saline chaser |
| Breathing | Shallow inspiratory breath hold |
| CT capability | |
| 128slice MDCT (minimum 64 slice MDCT accepted) | |
| Iterative reconstruction enabled | |
| Automatic mAs modulation enabled | |
| Automatic kV enabled | |

### 2.5. Primary outcomes

The primary outcome will be the 3-month incidence of VTE in pregnant patients in whom PE was excluded at baseline CTPA. VTE is defined as a symptomatic and objectively proven episode of PE and/or DVT during 3 months of follow-up and VTE related mortality during follow-up (see Table 4).

### 2.6. Secondary outcomes

Secondary outcomes include image quality and radiation dose outcomes (Table 5).

#### 2.6.1. Image quality outcomes

Image quality outcomes include the mean pulmonary trunk enhancement, signal to noise ratio (SNR) and contrast to noise ratio (CNR) achieved with this CTPA protocol. Additional outcomes used to assess image quality will include inter-reader variability, the number of indeterminate CTPA scans as a proportion of the total number of CTPAs performed and the average subjective image quality grade (as allocated by the CIAC).

Enhancement will be measured in Hounsfield Units (HU) using a region of interest of approximately $1cm^2$ placed within the main pulmonary artery (MPA) and latissimus dorsi (LD). Mean enhancement (Mean HU) and standard deviation (SD) will be recorded. Signal to noise ratio, will be calculated using SNR = (Mean MPA HU) / MPA SD. Contrast to noise ratio will be calculated as CNR = (Mean MPA HU – LD HU) / MPA SD.

#### 2.6.2. Radiation dose outcomes

Radiation dose outcomes will include the average maternal effective dose, breast organ dose and foetal dose (dose to uterus) and will be calculated using ImPACT CT dosimetry tool (version 1.0.4) based on Monte Carlo methods.

For a small number of patients wearing a breast shield during CTPA, direct measurements of skin dose at the maternal breast will be measured during the scan using thermoluminescent dosimeters (TLDs). For these patients, five TLD 100H dosimeters ($3 * 3 * 0.8$ mm) placed in protective polyvinyl chloride pockets are taped adjacent to the areolar region prior to exposure. TLDs are subsequently readout in a TLD reader (Harshaw 5500, Thermo Fisher Scientific).

### 2.7. Patient follow up

The number of patients with subsequent investigation for VTE, the number treated with anticoagulation in the interim, and the incidence

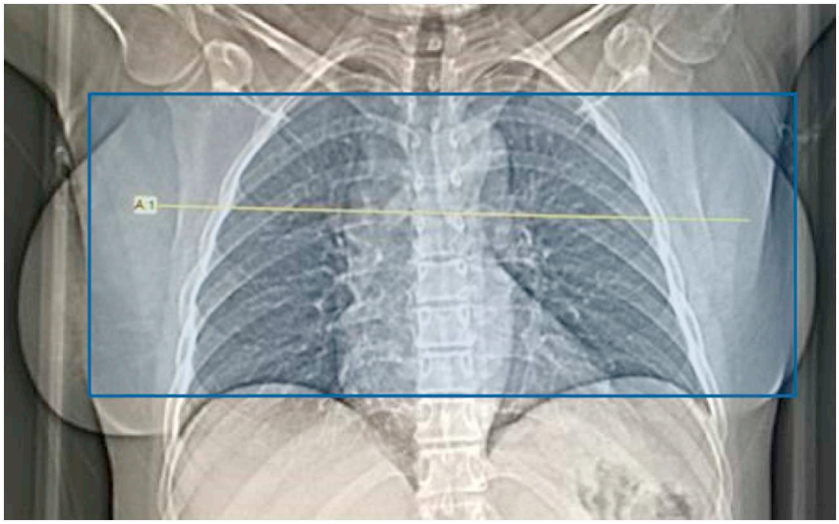


**Fig. 1.** The scan range extends from below the humeral heads to approximately 2 cm below the lowest dome of diaphragm.

**Table 4**
Primary outcome – VTE definition.

| Definition of VTE |
|---|
| 1. Lower extremity ultrasonography revealing non-compressibility at/above the popliteal vein tri-furcation |
| 2. CT venography revealing a constant intraluminal filling defect above the popliteal vein trifurcation |
| 3. CTPA revealing new intraluminal filling defect in a subsegmental or greater sized pulmonary artery |
| 4. Ventilation/perfusion scanning with a high probability of PE |
| 5. Pulmonary angiography demonstrating a new constant intraluminal filling defect or a cut off of a vessel |
| 6. Fatal PE discovered at autopsy or as judged by independent assessment. |

**Table 5**
Secondary outcomes.

| Secondary outcomes | |
|---|---|
| Image quality outcome | Radiation dose outcome |
| Mean pulmonary trunk enhancement (Hu) | Breast dose |
| SNR | Maternal effective dose |
| CNR | Foetal (uterine) dose |
| Inter-reader variability | Direct TLD measurement of breast skin dose (in a limited number of patients) |
| Number and proportion of indeterminate CTPAs | |
| Subjective image quality grade | |

of VTE is identified at follow up.

All patients have a specified scheduled contact by telephone 3 months from the time of their negative or indeterminate CTPA. During this contact any subsequent hospital attendance/investigation for recurrent VTE and any treatment with anticoagulation in the interim (including duration and indication), will be identified. Positive patient response to any of the above will prompt review of the patient's chart and subsequent imaging investigations. An independent adjudication committee incorporating two radiology consultants will review the subsequent imaging and adjudicate the diagnosis of VTE using the VTE definition in 2.3.

### 2.8. Sample size and statistical analysis

For patients with a negative or indeterminate CTPA result the 3 month pulmonary embolism incidence will be calculated and compared to reported incidence after negative pulmonary angiography. The negative predictive value will also be calculated. Based on a prevalence of 3%, estimated failure rate of 0.5%, an upper failure rate safety limit of 1.84%, and a loss-to-follow-up of 2%, the calculated sample size should be at least 464 participants at a significance level of 0.05 and power of 0.8. An adaptable study protocol will be employed such that the study will terminate, if the other endpoints also allow this, once the upper confidence interval below the consensus safety threshold is reached.

## 3. Rationale for particular aspects of OPTICA study

### 3.1. Absence of a direct comparator group

A lengthy recruitment phase is anticipated for this study given the relatively small numbers referred for evaluation of suspected PE in pregnancy and the comparatively large sample size required. In order to adequately assess the safety of CTPA in pregnancy the study aims to assess a single, specified protocol using a specific generation of CT technology. A lengthy recruitment limits the capacity to realise this as further advancements are made and radiology departments continue to upgrade their CT machines. Creating a comparator VQ group would ultimately double the recruitment time, thereby risking a heterogenous study comparing a range of CTPA protocols.

Given these considerations it was deemed preferable to evaluate the CTPA protocol in isolation and to compare to the most recent and relevant published lung scintigraphy data.

### 3.2. Choice of primary outcome

The primary outcome is the incidence of VTE during 3 months of follow-up for patients in whom the index CTPA was negative. Three months is an accepted timeframe within which to judge the performance of a negative index CTPA. This approach in assessing the safety of diagnostic tests in the evaluation of suspected PE is well established and has been applied to both conventional pulmonary angiography [31], CTPA [32] and clinical prediction rules [33–34].

This study focuses on the validity of negative CTPAs and the negative predictive value. The reason for this is two-fold; firstly the majority of CTPAs in pregnancy are negative which drives the decision to withhold anticoagulation and thus a false negative poses a significant risk to the patient. Secondly, the ability to determine if a patient is correctly or incorrectly labelled positive for PE, is limited by the fact that subsequent anticoagulation will confound any later rebuttal of an initial positive test result.

The PIOPED II trial used a composite reference test to confirm or rule out the diagnosis of PE. To do so, patients had additional imaging; either DSA, scintigraphy or in some cases doppler lower limb ultrasound, in order to establish a reference diagnosis against which the sensitivity and specificity of the CTPA could then be calculated [32]. CTPA is now the gold standard in the non-pregnant population. To subject pregnant patients to additional radiation in the form of VQ or DSA would be unethical and confer unnecessary risk to patient and foetus. This does, however, preclude assessment of sensitivity and specificity. Given the above considerations the incidence of PE at 3 months and subsequent calculation of negative predictive value are deemed appropriate and clinically relevant outcomes in place of sensitivity and specificity.

### 3.3. CTPA protocol adopted

The pre-defined CTPA protocol will be used for all patients in order to prevent study heterogeneity and allow adequate assessment of the described protocol. Use of a multi-detector CT (minimum 64-128slice) which is iterative reconstruction (IR) capable and auto-modulation enabled ensures the dose savings offered by the latest CT technology are incorporated into this study. Any additional study sites will have similar CT capabilities to ensure study homogeneity.

Further protocol adaptations include employing a smaller scan range, ensuring shallow held respiration and use of an 80 kV bolus-tracking component which is independent of the chosen kV for the diagnostic component of the study, all of which have been shown to reduce the overall dose or improve the image quality and therefore lower the risk of indeterminate CTPAs in pregnant patients [13,27–29].

#### 3.3.1. Scan range

The scan range extends from just below the humeral heads to approximately 2 cm below the dome of the lowest hemidiaphragm. This is smaller than that used in a normal CTPA in the general population which typically includes the entire thorax from above the apices to below the costophrenic angles. More aggressively truncated fields of view have been proposed, extending from the arch of the aorta to the dome of the diaphragm [29]. Shahir demonstrated retrospectively that a truncated scan range in 38 pregnant patients would have yielded no missed PEs while prospectively demonstrating in a non-pregnant cohort that a dose reduction of 71% could be achieved with an aggressive reduced range extending from aortic arch to the top of the diaphragm [29]. No study has prospectively demonstrated that a reduced scan range is safe. The argument for employing a smaller scan range is supported by the fact that tiny sub-segmental PEs, as found in the truncated peripheries of the lung, are often of debated clinical relevance. However, aggressively truncating the scan range poses obvious risks, particularly in a setting in which there is no clear definition of the location or level at which PEs can be safely left untreated. The authors feel that the proposed scan range offers a compromise between coverage and dose savings. Avoiding the shoulders provides a significant dose saving and the upper and lower extremes of the lungs excluded by this scan range would result in only subsegmental PE being potentially excluded from view, which are arguably of questionable clinical concern.

#### 3.3.2. Shallow respiration and IV contrast injection

Ensuring adequate opacification of the pulmonary vasculature is critical. The increased plasma volume of pregnant and postpartum patients and subsequent large pressure differential across the systemic veins puts these patients at increased risk of artefact compared to the non-pregnant population. Deep inspiration at time of contrast injection in this group results in a greater volume of unopacified blood from the IVC mixing with the contrast entering the right atrium from the SVC, with subsequent pockets of dilute contrast giving the impression of filling defects or causing an overall poor level of opacification. The instruction given to patients to ensure shallow respiration at time of contrast injection significantly limits the chance of this happening and thereby impacts on the image quality of the CTPA [13].

#### 3.3.3. Bolus monitoring technique

Lowering the kV setting employed for the bolus tracking component of the study, which triggers image capture at the moment of maximum opacification of the pulmonary vasculature, is a significant dose optimisation technique in the described protocol. It involves repeated scanning of a single thin slice of the chest which intersects the main pulmonary trunk, until detection of increased opacification indicates the CT scan should commence. Default factory settings risk unnecessary dose exposure however, and Mitchell et al. demonstrated that decreasing the beam energy from 100 kV to 80 kV for this component of the study, lowers the average breast dose from 2.25 mGy to 0.25 mGy for this part of the CTPA [27]. That's an 88% reduction in the breast dose attributable to this component of the CTPA in pregnant women.

Combined, the above strategies reflect a comprehensive approach to reducing the breast, maternal and foetal dose. It is important to note however, that radiation dose inevitably impacts image quality, with dose being reduced at the expense of increased noise and therefore reduced image quality. Chief among our considerations in optimising the CTPA protocol is to balance this trade-off such that radiation dose and the associated risk of breast cancer are lowered while maintaining an adequate image quality. The image quality variables (secondary outcomes) described above are used to ensure an acceptable standard is maintained. Ultimately this CTPA protocol is chosen, not to demonstrate the lowest dose achievable, but with the aim of balancing a reasonably low dose with the capacity to safely diagnose and out-rule PE in the pregnant population.

### 3.4. Shielding

Shielding aims to protect superficial organs by absorbing scatter radiation and lower energy photons from the beam which contribute more to dose than image quality. Both breast and abdominal shields have been employed in CTPA in pregnancy. Bismuth breast shields have been most studied in thoracic CT and have shown reductions in breast dose of up to 30–55% [35–39]. However beam hardening artefacts, streak artefact, and artefactually high CT numbers below the shield are among their disadvantages [37–38]. In recent years the popularity of shielding has waned as groups favour the adoption of low-dose CT techniques alone, given the potential negative impact on image quality when using shields and the comparable dose savings provided by low-dose CT strategies [40].

Phantom studies focused on combining both shielding and low-dose CT strategies have demonstrated that further dose savings can be achieved however. Hurwitz et al. demonstrated bismuth breast shields further reduced breast dose when combined with selective low-dose strategies (kVp of 120 and auto-modulation of tube current), without significantly impacting on noise levels [35]. Of note the OPTICA protocol typically employs a lower kV than this. Given that breast dose is the main concern regarding use of CTPA in pregnancy, assessing the potential of breast shields to further reduce breast dose when combined with a low dose CTPA protocol is of particular relevance.

There is limited assessment of the impact of combined strategies on image quality beyond phantom studies and most importantly, the impact of breast shields on image quality is likely to vary significantly depending on the low-dose protocol used as low-dose strategies become increasingly aggressive and themselves push the boundaries in terms of acceptable noise levels.

A phantom study performed in our institute to evaluate the impact of combined breast shields with our low-dose CTPA protocol demonstrated additional dose savings of approximately 50%, when measured by TLD dosimetry. Shields are known to increase noise levels most within the peripheral subcutaneous tissues directly under the shield,

while the increase in noise centrally is less pronounced; namely where segmental, lobar and main pulmonary arteries reside. Whether this less pronounced increase in noise centrally significantly impinges the diagnostic detail in low-dose CTPA protocols is unclear and is key in determining whether or not breast shields offer a net benefit in this setting. Given the limited capacity to assess image quality in phantom studies the final CTPA protocol was not adjusted to incorporate breast shields for all patients. Instead a small sub-group of patients will be offered the opportunity to wear breast shields during their scan. In these patients the breast dose will be measured at the skin and image quality will be further evaluated and compared to those without breast shields.

Abdominal shields have been shown to provide additional foetal dose savings when combined with a low-dose CTPA protocol [41], however due to the potential negative impact on image quality at the lung bases [42] particularly when sub-optimally positioned, and the already significantly low foetal doses achieved with CT reduction strategies abdominal shields are not incorporated into the OPTICA CTPA protocol.

## 4. Conclusion

In conclusion, we anticipate that this study will help shape the debate regarding the most appropriate first-line imaging investigation for suspected PE in pregnancy and the puerperium.

Current guidelines advocating the use of scintigraphy over CTPA remain focussed on radiation breast dose data which is out-dated and the debate hinges on the increased risk of breast cancer conferred by the greater breast dose of CTPA over scintigraphy. Lowering dose inherently reduces image quality, and so the proposed CTPA protocol aims to balance a reasonably low dose with the capacity to safely diagnose and out-rule PE in the pregnant population. This study is, to the authors knowledge, the first large scale prospective study evaluating the safety of low dose CTPA in this population. This will provide an up-to-date analysis of the breast dose achievable with modern CT technology and an evidence base for judging the appropriateness of modern CTPA protocols in this population.

Challenges going forward include meeting the required sample size in a timely manner, which will involve ensuring use of the same CTPA protocol across multiple sites nationally/internationally. Strict adherence to the protocol, particularly radiographer care in manually selecting the correct scan range for each patient will be important.

## Trial status

The OPTICA study is pending registration on ClinicalTrials.gov. Between May and November 2018, 14 patients have been recruited in 1 centre in Ireland.

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## Disclosure of conflicts of interest

There are no relevant conflicts of interest to disclose for any of the authors.

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