Randomized trial of Ventilation-Perfusion Scintigraphy versus Computed Tomography of the Pulmonary Arteries for Acute Kidney Injury Incidence

(Short Title: VQ CT Trial for AKI)

Study Protocol Version: 6.0

July 2, 2019

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List of Abbreviations

AKI = Acute Kidney Injury
AUROC = Area Under the Receive Operating Characteristic Curve
CIN = Contrast-Induced Nephropathy (additional terms used in cited literature)
CRF = Case Report Form
CT = Computed Tomography Imaging
CTPA = Computed Tomography Angiography of the Pulmonary Arteries
DVT = Deep Venous Thrombosis
$eGFR_{SCr}$ = estimated Glomerular Filtration Rate, calculated from serum creatinine[17]
$eGFR_{CYS}$ = estimated Glomerular Filtration Rate, calculated from serum Cystatin-C[17]
INPC = Indiana Network for Patient Care, Regenstrief Medical Records System
IRB = Institutional Review Board
IU = Indiana University, Indianapolis
IUH = Indiana University Health
IUSOM = Indiana University School of Medicine
PE = Pulmonary Embolism
MRI = Magnetic Resonance Imaging
NGAL = Neutrophil Gelatinase-Associated Lipocalin
REDCap = Research Electronic Data Capture, hosted by the Indiana CTSI
RR = Relative Risk ratio
SAE = Serious Adverse Event
VQ = Ventilation-Perfusion Lung Scintillation Imaging/ Ventilation-Perfusion Scintigraphy
VTE = Venous Thromboembolism (PE and/or DVT)
US = Extremity Doppler Ultrasonography of the Deep Veins

Document History

Document	Date of Issue	Summary of Change
Original Protocol	24 March 2016	IRB approval
V 2.0	01 June 2017	Revised to align with grant resubmission and standard NIH protocol format
V2.1	21 Feb 2017	Protocol title change Adding personnel
V 3.0	01 Aug 2017	Pre-Consent
V4.0	03 Oct 2017	Revision to baseline blood and urine collection Revision to exclusion criteria to remove "inability to obtain a venous blood for a baseline creatinine"
V5.0	20 FEB 2018	Exclusion criteria revision Study Project Manager contact information update Specimen collection and study procedures DSMB Charter revision
V6.0	19 Oct 2018	Inclusion criteria revision Adding another Hospital for enrollment Organization and Ineractions chart updated (pg 29)
V7.0	11 Jun 2019	Relying Sites: • Universtiy of Utah • Intermountain Healthcare

Statement of Compliance

The *VQ CT Trial for AKI* study has been designed and will be conducted in accordance with the following regulations, standards and guidance's to assure adequate protections for human subjects, and good clinical practices (GCPs). All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training. The study will be conducted in accordance with the following United States regulations:

- 45 CRF 46, US Code of Federal Regulations Applicable to Clinical Studies
- 21 CRF 50, Protections of Human Subjects
- 21 CFR 56, Institutional Review Boards
- Ethical Principles for Medical Research Involving Human Subjects ("Declaration of Helsinki"), 59th WMA General Assembly October, 2008

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Protocol Summary

Title	Randomized trial of Ventilation-Perfusion Scintigraphy versus Computed Tomography of the Pulmonary Arteries for Acute Kidney Injury Incidence
Précis	A total of 700 subjects will be enrolled. To measure the incidence of contrast-induced nephropathy (CIN), subjects (n = 600) with suspected pulmonary embolism (PE) will be prospectively randomized to CT of the pulmonary arteries (CTPA, iodinated contrast media exposure) or to ventilation-perfusion scintigraphy (VQ, unexposed control). To validate a risk-stratification tool for AKI, alone and in combination with acute-phase markers of renal dysfunction (Cystatin-C and NGAL) in both the exposure and unexposed controls, as well as, an additional non-randomized 100 subjects who will undergo CTPA for suspected PE. All subjects will followed for the development of acute kidney injury (AKI) occurring ≥ 48 hours and ≤168 hours following imaging and subsequent long-term outcomes.
Primary Study Objective	Compare the incidence of acute kidney injury (AKI) consistent with contrast-induced nephropathy (CIN) in 600 patients with suspected PE and an AKIrisk Score ≥2, randomized to CTPA (contrast media exposure) or VQ (unexposed control) imaging.
Secondary Study Objectives	1) Validate the AKIRisk score, alone and in combination with acute-phase markers of renal dysfunction (Cystatin-C and/or NGAL), to inform imaging strategies and reduce the risk of CIN. 2) Compare the incidence of AKI and subsequent severe health outcomes in patients exposed to iodinated contrast media and unexposed controls at 30-days and 1-year. 3) Measure the 30-day and 1-year incidence of VTE and subsequent severe health outcomes including outcomes related to VTE and VTE treatment
Safety Objectives	Compare the safety outcomes in both the CTPA and VQ groups including outcomes associated with imaging type, VTE (diagnosed and missed), and treatment of VTE occurring within 7 days of enrollment study imaging.
Primary Endpoint	AKI consistent with CIN, defined as an increase in creatinine ≥25% of baseline or an absolute increase in creatinine to ≥0.5 mg/dL ≥48 hours and ≤168 hours of the enrollment PE imaging study.
Safety Endpoints	Defined as one or more of the following events occuirng within 7 days (168 hours) of the enrollment PE imaging study: 1) Time to treatment of PE >8 hours defined as the time from study enrollment until initiation of anticoagulant therapy for PE. 2) Complications of PE imaging defined as one or more of the following occurring within 24 hours of the enrollment imaging study and requiring medical or surgical intervention: hypotension, difficulty breathing, acute pulmonary edema or hypervolemia, oral swelling, rash or puritis, abdominal pain, nausea or vomiting, altered mental status, or soft tissue contrast media or radio-isotope extravasation.

	3) Severe health outcomes defined as one or more of the following occurring within 168 hours of the enrollment imaging study: AKI (Acute Kidney Injury Network [AKIN] 1-3); Death (any cause), renal failure, or one or more of the following requiring medical or surgical intervention: acute myocardial infarction, stroke and/or other acute arterial vascular event, in any anatomic distribution, requiring medical or surgical intervention; death with renal injury as a significant contributor defined as obvious evidence of renal failure defined by worsening azotemia with complications of renal failure including oliguria, pulmonary edema, hyperkalemia, pericardial effusion, or the need to initiate renal replacement therapy before death; identification of a venous thromboembolism (VTE, PE and/or DVT) requiring medical or surgical intervention; death from VTE and/or hemorrhage requiring medical or surgical intervention as a result of treatment for VTE.
Tertiary End-points	Mid- (occuring within 30 days) and Long-term (occuring within 1 year) severe health outcomes
Number of Subjects	• A total of 700 subjects will be enrolled inclusive of 600 subjects that will be randomized to CTPA or VQ imaging and 100 non-randomized subjects that will undergo CTPA.
Inclusion Criteria	1) Age≥18 years CTPA ordered by the treating provider to evaluate PE. 2) Pre-test probability of PE ≤20% defined using the PE Pretest Consult Score. 3) For randomization to CTPA or VQ imaging (600 subjects): AKI risk ≥20% assessed by an AKIrisk Score ≥2 points 1) For non-randomized CTPA group (100 subjects): AKI risk <10% assessed by an AKIrisk Score <2 points.
Exclusion Criteria	1) A history of pulmonary surgery. 2) Findings on chest-radiograph that may limit the accuracy of VQ imaging for the detection of PE including air-space disease occupying more than 50% of the lung field, significant mass, or pleural effusion of significant volume or associated with low-lobe air-space diasease. 3) Clinical instability or other condition preventing randomization to CTPA or VQ imaging as reported by the treating provider. 4) Pregnancy or ≤48 hours post-partum. 5) Subject unavailability for reasonable follow-up including biological sample collection, creatinine measurement, and interview, such as an insecure residence, planned travel or absence, personal or professional obligations, incarceration, and/or other reason preventing follow-up, identified at enrollment. 6) Active renal replacement therapy (hemodialysis or peritoneal dialysis) within 30-days of enrollment or previous physician-directed plans to initiate dialysis within 30-days of the index visit. 7) Prior renal transplant or planned within 30-days of enrollment.

	Intravascular iodinated contrast media administration within 14 days prior to enrollment or planned within 7 days of enrollment.
Population characteristics	We expect approximately 60% women and 35-50% minority representation, and 1-3% of Hispanic/Latino origin.
Study Sites	We will enroll patients at 5 sites. IUH Methodist Hospital (also provides emergency care to IUH Universtiy Hospital), Eskenazi Hospital, IUH Ball Memorial Hospital, Univestiy of Utah, and Intermountain Healthcare
Description of Study Intervention	Subjects will undergo 1 of 2 standard of care diagnostic imaging studies for suspected pulmonary embolism. Study Inclusion and Exclusion Criteria specifically select patients that are appropriate for evaluation by either imaging study.
Study Duration	Study enrollment and follow-up for primary and outcome meaures will be completed within 4 years. Subject participation will last for 1 year.

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1.Background Information and Scientific Rationale

1.1 Study Overview

Despite widespread use of less nephrotoxic, contemporary iodinated contrast media agents, contrast-induced nephropathy (CIN) remains a leading cause of acute kidney injury (AKI), occurring as frequently now as in the 1970s.[1] Human exposure to iodinated contrast media agents is now a large and rapidly growing public health problem: over 40 million patients are exposed annually with CT imaging studies.[2] The rate of CT imaging has increased exponentially over the past decade, and >25% of exposures now occur in the emergency care setting.[3,4] Patients evaluated for pulmonary embolism (PE) are among the mostly likely to be exposed: >10% of the patients evaluated for chest symptoms in the emergency care setting undergo contrast-enhanced CT of the pulmonary arteries (CTPA).[5] Less than 1% of these patients, and only who physicians considered to be at the most extreme risk of CIN, undergo non-contrast imaging for PE, namely ventilation-perfusion scintigraphy (VQ).[4-6]

Preliminary work demonstrates the following:

1) More than 15% of patients that undergo CTPA develop AKI consistent with CIN.[7]
2) An elevated creatinine (eGFR <60 ml/min/m^2) has poor sensitivity (13%) for the prediction of CIN.[8-10]
3) Even after adjusting for age and co-morbidities, patients who develop CIN after contrast-enhanced CT have a 2-fold increased risk of death, renal failure and major cardiovascular events over the next year.[11]

These findings motivated the applicant to derive a clinical prediction rule, the "AKIrisk Score:" age ≥50 years (1 point), HIV (1 point), coronary artery disease (1 point), diastolic hypertension ≥100 mmHg (1 point), and glycosuria ≥250 mg/dL (2 points). This score is a significant improvement over pre-CT creatinine screening: AUROC 0.75; AKIrisk Score ≥2 points with 60% sensitivity and predictive value positive of 27%.[8] Preliminary data also demonstrate that acute-phase biomarkers of renal dysfunction, Cystatin-C and Neutrophil Gelatinase-Associated Lipocalin (NGAL), improve the predictive accuracy for CIN.[9,10]

As a specialty, emergency physicians are particularly facile with the use of clinical decision rules.[12] In fact, clinical decision rules guiding the use of CTPA imaging are among the most well-known and widely adopted in emergency care practice.[12] However, current emergency medicine PE clinical decision rules do not consider CIN from CTPA imaging, resulting in both a lack of knowledge of the risk and subsequent outcomes of CIN, and the underuse of imaging strategies that prevent contrast media exposure.[13]

1.2 Study Hypothesis

The study hypothesis is that while a clinical decision rule more accurately risk-stratifies patients for AKI than creatinine screening, subsequent avoidance of exposure to contemporary contrast media agents does not alter overall AKI-risk. The alternative study hypothesis is that contrast media exposure is associated with an increased risk of AKI and the AKIrisk Score can be used to guide selective VQ imaging and reduce CIN in patients evaluated for PE in the emergency care setting.

This project will accomplish the following ***specific aims***:

1) In 100 patients undergoing CTPA for suspected PE, test the accuracy of a AKIrisk Score <2 to predict a CIN-risk <10%.
2) Test if the use of acute-phase markers of renal dysfunction, Cystatin-C and/or NGAL, improves the predictive accuracy of the AKIrisk Score.
3) Compare the incidence of AKI consistent with CIN in 600 patients with suspected PE and a AKIrisk Score ≥2, randomized to standard CTPA (contrast media exposure) or VQ (unexposed control) imaging.

The ***outcomes*** of this research will 1) Validate effective methods of risk-stratifying patients for AKI-risk in the heterogeneous, real-world emergency care setting; and 2) Provide the rigorous evidence needed to change imaging practices and either a) more effectively prevent CIN OR b) Improve the utilization of imaging resources and avoid delays currently caused by unnecessary screening and prevention practices. These outcomes are central to future advances in AKI prevention in the emergency care setting and to optimizing current imaging practices; current time and resource consuming CIN-prevention methods characteristic of current clinical practice

will not change without prospective validation with a randomized, controlled trial.[1, 3, 4] The ***specific translational impacts*** include 1) Quantification of the risk of AKI from contrast media exposure in the emergency care setting, 2) Validation of a clinical decision rule for the prediction of with either multi-cause AKI or CIN specifically, and 3) Vetting of two acute phase markers of renal dysfunction for use in the real-world, emergency care setting.

1.3 BACKGROUND

Patient exposures to intravascular iodinated contrast media are increasing rapidly. Over the past 40 years, iodinated contrast media agents have evolved from the highly toxic, high-osmolar, high-ionic agents to the contemporary low-osmolar, nonionic agents used throughout the United States. However, 40 years ago, the number of cardiac catheterizations and computed tomography (CT) imaging studies performed in the United States annually could be measured in the thousands. While the inherent toxicity of contrast media has improved, the use of these agents has increased exponentially. Currently, approximately 2 million cardiac catheterization procedures and over 70 million CT imaging studies are performed in the United States annually.[2] Over 10% of the 117 million patients treated annually in the emergency care setting undergo CT imaging annually.[3,4] Thus, quantifying the risk of contrast media exposure from CT imaging in the emergency care setting, specifically the risk of Contrast-Induced Nephropathy (CIN), is essential.

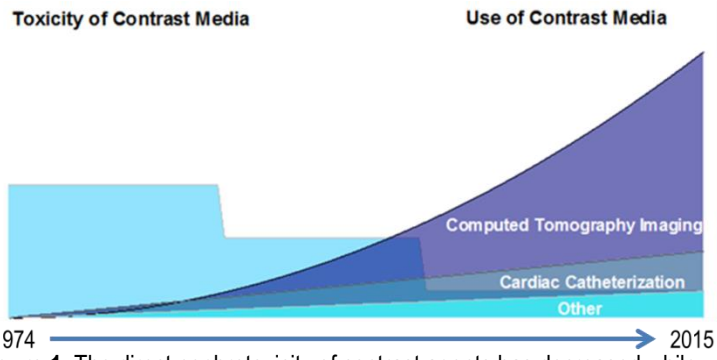


Figure 1. The direct nephrotoxicity of contrast agents has decreased while exposures have dramatically increased. Contrast-enhanced CT imaging, particularly from the emergency care setting, is now the major source of patient exposures to contrast media agents.

1.4 RATIONALE

Over the past 2 decades, contrast-induced nephropathy (CIN) has been consistently identified as a leading cause of acute kidney injury (AKI).[1,18] Published literature, including data from the PI, demonstrate that 5 to 25% of patients, in hospital and ambulatory settings, exposed to contemporary contrast media agents develop CIN leading to severe outcomes.[1,19-27] However, the literature is replete with directly conflicting evidence of *relevance* of contrast exposure to the development of AKI:[14,15,28-30]

> "Decreased renal perfusion, medications, surgery, and radiographic contrast media were the most common causes of hospital-acquired renal insufficiency (HARI).....Radiographic contrast media were responsible for 11% of episodes [of HARI], a percentage that is essentially unchanged from 1979."[1]

> "…our study represents the first comprehensive systematic review and meta-analysis focused on studies in which the investigators compared the risk of AKI between patients who received intravenous iodinated contrast medium and patients who either underwent a related non-enhanced imaging study or did not undergo an imaging study….These results show that the RR [relative risk] of AKI was similar among patients who received intravenous contrast medium, as compared with the control groups of patients who did not receive intravenous contrast medium….. As anticipated, there were no randomized controlled trials in which the effects of contrast medium administration on the incidence of AKI were studied."[31]

> "Contrast Induced- Acute Kidney Injury (CI-AKI) is not simply a "transient, benign creatinopathy," but rather a direct cause of worsening chronic renal function and increased cardiovascular events, institutions should now consider prevention of CI-AKI a quality improvement goal….. We await conclusive data from randomized clinical trials….."[22]

> "Without a control group of unexposed patients, the association of AKI with contrast administration is possibly confounded by the independent risks for renal failure seen in all hospitalized patients."[15]

> "Our findings provide additional evidence that the administration of intravenous contrast material does not increase the risk of AKI, even in patients with substantially compromised renal function."[16*]

Despite a lack of definitive evidence, significant effort and costs are associated with both the prevention and treatment of CIN. Precedent literature attributes CIN with marked increases in hospital mortality, prolonged hospitalization and increased costs.[1,33,34] Over one quarter of all laboratory testing in the emergency care setting alone is performed with the express purpose of identifying patients at increased risk of CIN.[35] National and international cardiology and radiology organizations continue to invest resources into developing and promoting national guidelines aimed at reducing CIN.[36-42] However, research aimed at quantifying the potential impact of reducing contrast media exposure is limited to a single active meta-analysis protocol.[30] There are no active, randomized trials that address this long-standing controversy. (www.clinicaltrials.gov, accessed 3/10/2015).

The following conditions are necessary for a trial of this type:

1) Prospective Design: With CIN, the characteristic rise in creatinine does not peak for 3 to 5 days, or longer in more severe cases.[43,44] Similarly, the change in creatinine needed to identify other causes of AKI is variable. Moreover, routine, compulsory post-exposure surveillance for AKI is not currently the standard of care, or even common practice, especially in the outpatient and reduced-hospital stay settings. As such, retrospective, post-exposure data are likely to severely and unpredictably underestimate both the relative contribution of CIN and other causes of AKI.[14,16,32,45]
2) Controlled, Randomized Exposure: Contrast media is administered for specific clinical indications; populations undergoing contrast-enhanced and non-contrasted diagnostic studies are distinct, and differ significantly in terms of acute illness state and risk of CIN or other AKI. Thus, unstructured comparisons between these populations are severely limited.
3) Comparison of Clinically Equivalent Diagnostic Imaging Tests: The standard contrast-enhanced study(ies) and the non-contrast alternative(s) must have equivalent diagnostic accuracy and cannot carry significantly higher risk of adverse events (e.g. radiation exposure, invasiveness, etc.).
4) Well Defined Study Population: Ideally, the selected contrast-enhanced and the non-contrast alternative(s) would result in the following: A) A well-defined patient population undergoing evaluation for a single, unified clinical disease with predictable risk and expected outcomes; B)The presence or absence of the disease in question would have minimal, if any, effect on AKI risk, and; C) At the completion of diagnostic testing (contrast-enhanced imaging or a non-contrast alternative), both groups would have a low and equal risk of subsequent nephrotoxic events (e.g. sepsis, surgery, etc.) or drugs exposures, including additional contrast media administration.
5) Common Diagnostic Study: To achieve the necessary study accrual, both the contrast-enhanced study and the non-contrast alternative must have reasonable availability and be performed commonly enough that treating physicians are familiar with the use of both imaging strategies.

The only feasible approach to quantifying the contribution of limiting contrast media exposure to the overall risk of AKI, is to prospectively randomize patients evaluated for acute pulmonary embolism (PE) to CT of the pulmonary arteries (CTPA, contrast exposure group) or ventilation-perfusion scintigraphy (VQ, non-contrast control). Potential alternative approaches are compared in Table 1. The PI and her collaborator (Kline) have prior experience and years of practice-changing research in the diagnostic evaluation of pulmonary embolism (PE).[7,46-48] As a result of their prior work, they are able to closely define the patient population that can be safely randomized. Preliminary data from the PI demonstrates that at least 15% of patients evaluated for PE with a CTPA go on to develop AKI consistent with CIN and subsequent severe outcomes.[7,11] However, in patients who are at low- and moderate-risk of PE (pre-test risk of PE ≤20%), a PE itself does not raise or lower the risk of CIN (see Preliminary Data). For low- and moderate-risk patients, CTPA and VQ (in combination with selected extremity venous ultrasonography [US]) are diagnostically equivalent in confirming or excluding acute PE.[49-52] Compared to <3% in 2001, over 10% of patients evaluated for chest pain in the emergency care setting undergo CTPA.[5] As a result, CTPA is the third most common diagnostic CT imaging study performed in the emergency care setting.[4] Both tests are minimally invasive, requiring only peripheral intravenous catheter placement and positioning for chest imaging. Aside from the risk of CIN associated with CTPA, the risks of both imaging

strategies are low and essentially limited to the risks associated with ionizing radiation. Published data and expert opinion agree that the risk of radiation exposure with VQ is the same or less than CTPA.[50,53,54] The major advantage to CTPA is not directly related to patient benefit; VQ imaging is simply more resource intensive (preparation of the radioisotope, maintenance of a nuclear imaging facility, and need for a specialty technician and radiologists) and the results of the test are more difficult to interpret.[6] In fact, perceived risk of CIN is the single most important motivation to select VQ over CTPA in the clinical setting.[6] As such, treating physicians are facile with the use of both diagnostic modalities.[51,55]

Table 1. The only feasible approach to quantifying the exact contribution of contrast media exposure to overall risk of acute kidney injury (AKI), is to randomize patients evaluated for pulmonary embolism (PE) to CT of the pulmonary arteries (CTPA, contrast exposure group) or ventilation-perfusion scintigraphy (VQ, unexposed control).

Contrast-Enhanced Study	Non-Contrast Alternative(s)	Clinical Indication(s)	Potential Study Accrual	Applicability to Primary Study Objective
Cerebral CT Angiography *OR* Formal Angiography	MRI	Cerebral Aneurysm Cerebral Dissection Occlusive Thrombus Vasculitis	Insufficient	Inappropriate • MRI has lower sensitivity. • Formal angiography is more invasive
Body/Peripheral CT Angiography *OR* Formal Angiography	Arterial Ultrasound	Limb Ischemia Mesenteric Ischemia Aortic Aneurysm Aortic Dissection	Insufficient	Inappropriate • Ultrasound lacks availability and diagnostic accuracy. • Formal angiography is more invasive.
Body CT	Soft-Tissue Ultrasound *OR* MRI	Soft Tissue Lesions/Masses Deep Space Abscesses Intestinal Obstruction/Perforation Solid Organ Injury Abdominal/Pelvic Complaints	Sufficient	Inappropriate • Unpredictable population heterogeneity, including nephrotoxic exposures. • Ultrasound and MRI have variable diagnostic accuracy. • Treating physicians not facile with alterative imaging. ➢ Many patients will require contrast-enhanced CT after non-contrast imaging (not predictable).
Coronary CT *OR* Coronary Angiography	Non-Invasive Cardiac Stress Testing *OR* MRI	Acute Coronary Syndromes	Sufficient	Inappropriate • Variable diagnostic accuracy • Patients at highest risk of AKI will require angiography, regardless of randomization.
CT of the Pulmonary Arteries (CTPA)	**Ventilation-Perfusion Scintigraphy** (VQ)	**Single, Well-Defined Indication:** Pulmonary Embolism	**Sufficient**	**Appropriate** • Well-defined population[47,56-58] • Diagnostically equivalent tests[49] • Equal risk of radiation exposure[50,53,54] • Familiar to treating physicians[51,55] • AKI risk independent of PE outcome

AKI = acute kidney injury; CT= computed tomography imaging; MRI=magnetic resonance imaging; VQ = ventilation-perfusion lung scintigraphy

1.5 PRELIMINARY DATA

Over 10% of patients develop an AKI consistent with CIN after contrast-enhanced CT imaging. These patients are also at significantly increased risk of severe outcomes over the following year. In the largest cohort published to date, the PI and her collaborator (Kline), prospectively followed 633 unselected patients undergoing contrast-enhanced CT imaging for the outcomes of AKI consistent with CIN and 1-year major adverse outcomes including death, renal failure and cardiovascular events (stroke, myocardial infarction, other vascular events requiring

medical or surgical intervention). Notably, this is a larger cohort than that planned for the proposed study. The incidence of CIN was over 10% in all patients,[20] and 15% in the population undergoing CTPA.[7] There was no difference in the rate of CIN among inpatients compared to patients discharged after imaging. After adjusting for age and comorbidities, the development of CIN was associated with a markedly increased risk of death (Figure 2)[7,11,20] and an increased risk of major adverse events, including renal failure and arterial vascular events requiring intervention, at 1-year (adjusted RR 2.36 95%CI 1.5 to 3.7). The risk of severe outcomes increased with severity of AKI.[11,20]

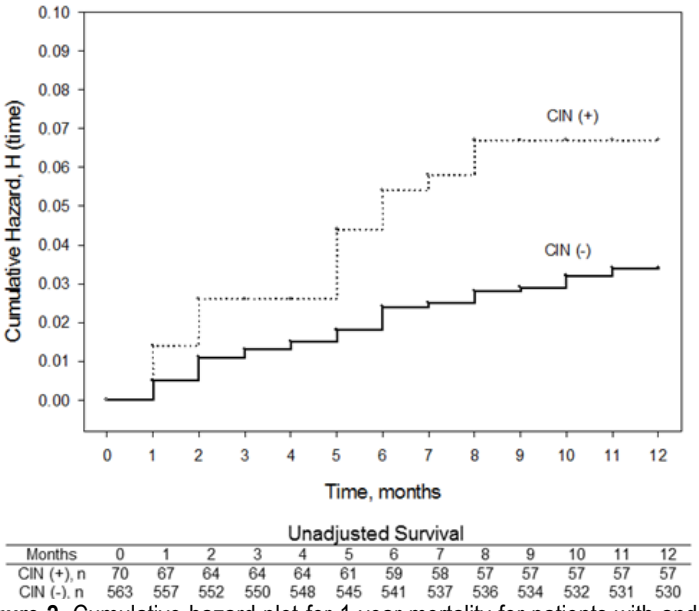


Figure 2. Cumulative hazard plot for 1-year mortality for patients with and without Contrast-Induced Nephropathy (CIN), adjusted for age and the presence of an active malignancy at the time of enrolment. ($p < 0.01$).

The study investigators have previously developed methods of identifying patients evaluated for PE that can be safely randomized: A co-investigator for this study (Kline) derived and validated an attribute matching method to individually quantify the pre-test probability of venous thromboembolism (VTE, PE or deep venous thrombosis [DVT]), PE PreTest Consult Score (PreTest Consult©; v2.1Q; CP Diagnostics, LLC; Charlotte, NC).[47,56-59] (Figure 3) The PE PreTest Consult Score leverages prospective data from over 8,000 patients evaluated for PE, by CTPA or VQ, at 7 medical centers (6 in the United States and 1 in New Zealand) and is openly available (http://pretestconsult.com/v21/pe). Importantly, this method of assessing pre-test risk of VTE is *well-accepted and used by physicians at medical centers throughout the United States*.[12]

The 45-day incidence of VTE in patients with a calculated pre-test risk between 2.5% and 20% was 3%. Importantly, the accepted test threshold prompting imaging for suspected PE is very low: only 2.5%.[13,48] As such, <15% of patients who underwent imaging for suspected PE ultimately were ultimately diagnosed with VTE. Pre and post-CTPA creatinine data were available for 30% of a validation subset (834 patients from 4 institutions)

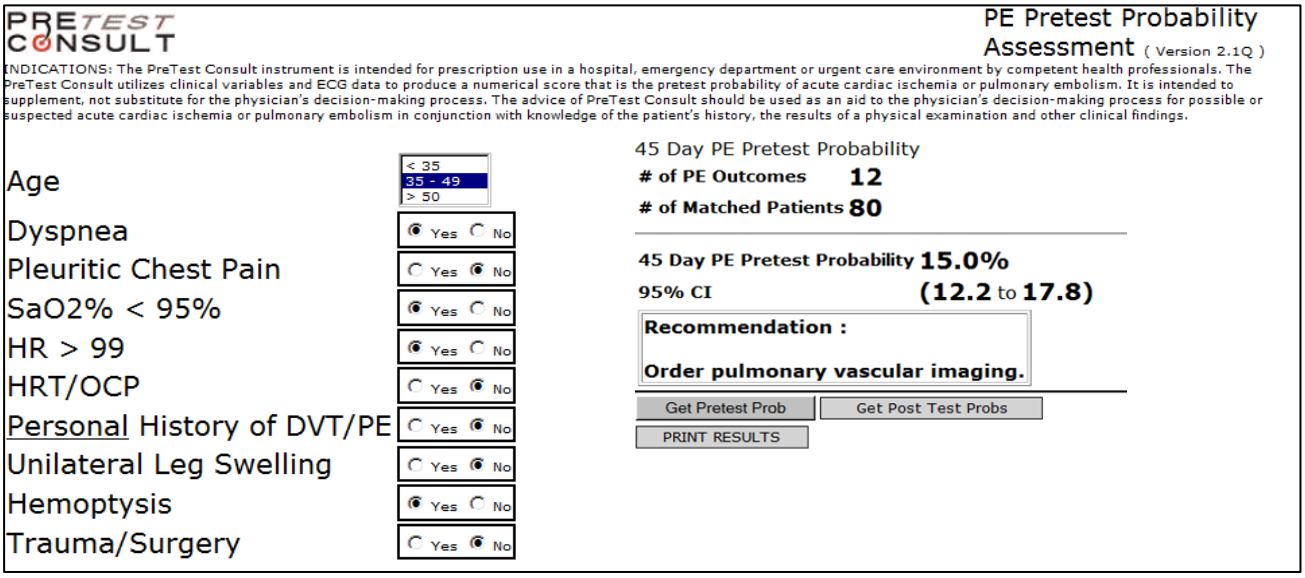


Figure 3. Example output of the PE PreTest Consult Score (http://pretestconsult.com/v21/pe), which allows clinicians to calculate the point-estimate of an individual patient's pre-test probability of pulmonary embolism, at the bedside, using an attribute matching method leveraging over 2 decades of data, from over 8,000 patients evaluated at 7 medical centers, developed by a co-investigator (Kline) along with the PI.[47,56-59]

evaluated simultaneously for both suspicion of acute coronary syndromes and PE. In patients at low and moderate risk of PE (pre-test VTE risk ≤20%), *the rate of AKI consistent with CIN, did not differ with the presence (9%) or absence (8%) of a VTE*.

The PI has developed methods if risk-stratifying patients for CIN in the emergency care setting: Using data from her contrast-enhanced CT cohort of patients treated in the emergency care setting, the PI evaluated over 100 literature derived risk factors (at varying thresholds) for CIN[18,23,28,41,60-83] and derived the AKIrisk Score: 2 points for glycosuria on urine dipstick; and 1 point each for Age ≥50 years, measured diastolic blood pressure ≥100 mmHg, history of HIV or AIDS, and a history of coronary artery disease.[8] Importantly, an elevated creatinine (SCr), corresponding to an estimated glomerular filtrate rate ($eGFR_{SCr}$) ≤60 ml/min/m^2,[17] did not accurately risk-stratify patients for CIN: sensitivity 13%, area under the receiver operating characteristic curve (AUROC) 0.55.[9,10] In comparison, a AKIrisk Score of ≥2 points more accurately predicted CIN: sensitivity 56% (95% CI 43 to 68%), specificity 81% (95% CI 77 to 84%), AUROC of 0.74 (95% CI 0.68 to 0.81) and positive predictive value (27%, 95%CI 20 to 34%).[8-10] (Figure 4)

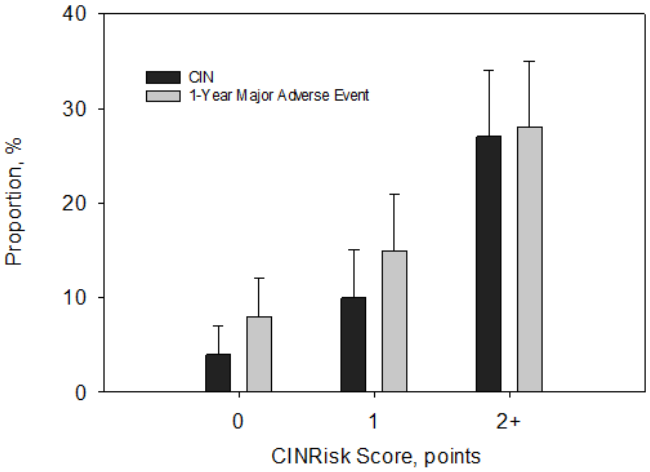


Figure 4. Outcomes (prospective) for patients (n=633) undergoing contrast-enhanced CT imaging, risk-stratified by the AKIrisk Score. Major Adverse Events were as defined as death, renal failure, acute myocardial infarction, cerebral vascular accident and/or other arterial vascular event requiring surgical or medial intervention.

In the same prospective cohort, the PI has also tested the prognostic accuracy of two emerging biomarkers of acute-phase renal dysfunction in her CT cohort, Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Cystatin-C ($eGFR_{CYS}$, expressed as eGFR calculated using Cystatin-C[17]), alone and in combination with the AKIrisk Score. (Table 2.)[9,10]

As proof of concept, preliminary data also indicate that exposure to contrast media with CTPA in associated with an increased risk of AKI: The PI examined retrospective data for 100 randomly selected patients (50 male and 50 female) at low or moderate risk of PE, with VQ imaging for suspected PE and 100 matched controls (age, gender, Black race, and $eGFR_{SCr}$) with CTPA imaging between January and December of 2014.

Table 2. Comparison of the predictive accuracy for contrast-induced nephropathy (CIN) of Neutrophil Gelatinase-Associated Lipocalin (NGAL, alone and when included in the AKIrisk Score) and Cystatin-C (expressed as $eGFR_{CYS}$) to creatinine (expressed as $eGFR_{SCr}$).

Factor	Threshold	AUROC	Sensitivity	Specificity
$eGFR_{SCr}$	≤60ml/min/m^2	0.55 (0.47 to 0.63)	13% (5 to 23%)	87% (83 to 90%)
NGAL	≥ 100 mg/dL	0.68 (0.60 to 0.75)	80% (64 to 91%)	63% (57 to 69%)
NGAL AKIrisk Score*	≥ 3 points	0.82 (0.75 to 0.89)	90% (76 to 97%)	60% (54 to 65%)
$eGFR_{CYS}$†	≤60ml/min/m^2	0.76 (0.56 to 0.95)	65% (52 to 77%)	88% (84 to 90%)

*NGAL AKIrisk Score: NGAL≥100 ng/dL 3 points, and 1 point each for age ≥50 years, diastolic hypertension ≥100 mmHg, and diabetes mellitus.
†There was no improvement in prognostic accuracy when $eGFR_{CYS}$ was combined with the AKIrisk Score.

Dialysis dependent patients and renal transplant patients were excluded, as were patients who were exposed to intravascular contrast media, within 30 days prior to, or within 7 days following, the selected PE imaging study (VQ or CTPA). Findings are summarized in Table 3. Importantly, the rate of intermediate risk VQ was only 3% and the detection rate of acute PE by VQ was not lower than CTPA. Because physician assessment of increased risk of CIN is the primary reason that patients undergo VQ imaging rather than CTPA,[6] it is not surprising that a larger proportion of patients in the VQ group had a AKIrisk Score ≥2. Because VQ is usually reserved for patients at the upper-limit of overall risk AKI (CIN and other additional causes), we expect that the incidence of AKI in the

group randomized to VQ will be lower in the proposed study. Importantly, despite a lower physician-estimated (unstructured) risk, the rate of AKI was significantly higher in the CTPA group.

Table 3. Preliminary data demonstrating an increased risk of acute kidney injury (AKI) with contrast media exposure.

	CTPA Imaging N=100* *Exposed to Contrast Media*	**VQ Imaging N=100*** *Unexposed Control*
AKIrisk Score ≥2 points, % (95% CI)	72 (62 to 81)	86 (77 to 92)
Acute Pulmonary Embolism on Imaging Study, % (95% CI)	8 (4 to 15)	10 (5 to 18)†
Acute Kidney Injury, % (95% CI)	32 (23 to 42)	6 (2 to 13)

*Median Age 73 years (IQR 20), Black Race 42%, Median eGFR 37 ml/min/m^2 (IQR 28)

† VQ imaging studies interpreted as intermediate risk for acute pulmonary embolism in an additional 3 patients.

1.6 Known Potential Risks

400 patients enrolled in this study will go on to complete the CTPA (300 with a AKIrisk Score ≥2 after random assignment and 100 with a AKIrisk Score <2) and, as ordered, and will have an exposure to contrast media as a result of usual care. The remaining 300 patients will undergo VQ imaging, which has equivalent diagnostic accuracy for PE (in patients with a pre-imaging risk of PE ≤20% and a normal chest radiograph) and the same or lower risks of exposure to ionizing radiation as CTPA. [50,53,54] Patients may provide a urine sample and could have as many as two blood draws, which is associated with minimal risk. Importantly, these patients will already have intravenous access placed in preparation for the diagnostic imaging, as part of their usual medical care. Thus, for the majority of patients, the first blood sample may not require an additional needle stick.

The decision of whether or not to enroll could induce psychic stress to the patient at a time when they are already afraid. The PI and co-investigator (Dr. Kline) have conducted telephone follow-up with patients treated in the emergency care setting as proposed here on over 4,000 patients with no patient complaints or evidence of distress.[11,20,47,103] From prior experience, we estimate that 60% of patients will have primary family members present at the time of informed consent. Patients will be informed on the potential increase in time spent in the emergency department during the informed consent process. There may also be a potential loss of confidentiality. Clinical data will be collected by trained study personnel who are listed on the IRB approved protocol and all data will be kept in a secure electronic format. The PI, research coordinator and data analyst. Research assistants will have limited access and only as needed to assist with screening, enrollment, and coordination of follow-up. We will redact PHI from records that might be examined by non-study personnel.

We will record and keep results of clinical data, including literature-derived risk factors for CIN, [18, 23, 28, 41, 58-81] as reported in the electronic medical record, reported by the clinical team, and from the patient themselves (follow-up interviews), using study-specific data collection template created and maintained on REDCap. REDCap (Research Electronic Data Capture, hosted by the Indiana CTSI) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. We will request contact information (address, telephone number[s], email) which will be destroyed after initial follow-up and creatinine measurement, and, if applicable, notification of patients of CIN outcome, is complete. We will also obtain and store blood and urine samples for Cystatin-C and NGAL measurements. We will obtain and keep medical records, study case report forms (CRF).

As with all patients evaluated for PE in the emergency care setting, patients will remain in the care of emergency physicians throughout their emergency department stay, including completion of the PE imaging study, including reporting of PE imaging results and associated treatment, until hospital admission and transfer of care or discharge, as per usual care. The follow-up interview and blood-draw will occur in the emergency care or inpatient setting, using the standard patient-care facilities.

Specifically in this study, patients with a risk of PE ≤20%, VQ and CTPA have comparable diagnostic accuracy in the identification and exclusion of acute PE.[49-52] Patients with air-space disease occupying more than 50% of the lung field, significant mass, or pleural effusion of significant volume or associated with low-lobe air-space diasease are more likely to have an intermediate-risk VQ imaging study. Not only is it standard of care to obtain a chest radiograph to evaluate patients for chest symptoms prior to proceeding to CTPA, it is also standard of care to screen patients for appropriateness for VQ with a chest radiograph, as we plan for our study. In some cases, the treating physician may also suspect pulmonary disease, outside of PE and not visualized on chest radiograph (ordered for standard care). In these cases and at the discretion of the treating physician, patients in the VQ arm will have a non-contrast CT of the chest or single-photon emission computed tomography (SPECT) imaging may also be used. Treating physicians will be encouraged to discuss such cases with the consulting radiologist. This approach is consistent with the usual standard of care for patients evaluated by VQ. Similarly, for patients who are immediately clinically unstable, VQ imaging is not appropriate. These patients are also excluded from this study.

1.7 Known Potential Benefits

All patients enrolled in this study would have otherwise undergone CTPA imaging as a part of their usual care. Approximately half of patients enrolled (n = 300) will undergo VQ imaging which is associated with a risk of exposure to is comparable and potentially lower that of CTPA[50,53,54] but avoids an exposure to iodinated contrast media. Given the significant long-term consequences of even a single episode of CIN,[11,28] the benefit may be improved methods of identifying patients at risk, and then preventing CIN and subsequent severe outcomes. Published data suggests that VQ may also decrease the risk of hemorrhage from unnecessary exposure to long-term anticoagulant therapy, as a result of over-diagnosis of small subsegmental PE.[49-52] At minimum, prior published data clearly demonstrate that the risk of missed VTE with VQ (and selective US) is not increased over CTPA.[49-52] Our preliminary data are consistent with published results. In addition, VQ imaging is associated with the same risk of exposure to ionizing radiation as CTPA, but avoids exposure to iodinated contrast media. Thus, patients participating in this study will undergo one of two standard of care imaging studies for PE. Patients who choose not to participate will undergo CTPA testing as planned. Participants will have the opportunity to complete CTPA imaging as planned or undergo VQ imaging, which has the same, or potentially less overall risk than CTPA. All patients will have the opportunity for post-imaging surveillance for AKI, which is not routinely performed. Patients who do develop AKI, based on follow-up creatinine screening at 2-7 days, will have the opportunity to seek follow-up care.

2. Study Objectives

2.1 Primary Objectives

The primary study objective is to compare the incidence of acute kidney injury (AKI) consistent with contrast-induced nephropathy (CIN) in 600 patients with suspected PE and an AKIrisk Score ≥2, 300 randomized to CTPA (contrast media exposure) and 300 randomized to VQ (unexposed control) imaging. The primary outcome measure, AKI consistent with CIN. The primary outcome, AKI consistent with CIN, will be defined in both the exposed (CTPA) and un-exposed (VQ) groups using the standard literature definition for CIN:[69] an increase in creatinine ≥25% of baseline or an absolute increase in creatinine of ≥0.5 mg/dL ≥48 hours and ≤168 hours of the enrollment PE imaging study.

Notably, while creatinine remains the clinical standard for identifying AKI of all types, a measurable rise in creatinine may not occur for hours to days after the initial injury. In the case of CIN, the typical peak in creatinine does not occur for 3 to 5 days, with recovery to baseline or new baseline in 7 to 14 days.[43,44] As with other forms of AKI, in patients with normal or mild impaired renal function, a more severe injury and longer time frame are needed to detect a rise in creatinine indicative of AKI. Indeed, while many studies of CIN limit the follow-up period to 72 hours, this approach may miss 10 to 60% of cases, especially in heterogeneous populations.[43,91-95] Even using a follow-up method that allows for variable follow-up within a 7 day period, we acknowledge that our study design is also more likely to miss cases rather than over-estimate the incidence of AKI.[7,20 11] Our goal is to define

the potential to reduce AKI by limiting contrast media exposure. Thus, a prospective, randomized study is required.

We acknowledge that the primary outcome of CIN is likely to occur in patients that remain asymptomatic, as expected for the first stages of AKI. We do plan to measure and report patient-center, symptomatic, severe outcomes (see *Secondary Endpoints*) occurring within 1-year. Aside from our own preliminary data,[7,11,20] there are no consistent, published, prospective data, with sufficient long-term follow-up,[32,45] in the emergency care setting, or other comparable heterogeneous, ambulatory population (pre-exposure renal function ranging from normal to impaired). Moreover, there are no prospective, controlled data, in any setting, that can be used to adequately design (and determine the sample size for) a study primarily aimed at measuring the long-term, severe outcomes subsequent to CIN. Hence, we have focused on the first phase of AKI, CIN, as the primary outcome, and plan to use the data to inform future research quantifying the effect of selected contrast media exposure on the prevention of long-term severe outcomes subsequent to the development of CIN.

To determine sample size, we conservatively estimated an overall AKI rate of <20%. The sample size was determined based on a Chi-square test (two-tailed, 5% type I error). A sample size of 188 in the CTPA group (exposed) and 269 in the VQ group (unexposed) in each group will have 80% power to detect an absolute difference of 10%. Assuming up to 5% screening and randomization failures (patients assigned to VQ, but undergo CTPA imaging) and a 30% dropout rate, [7,11,20,53,89] we will recruit 300 subjects per group. (nQuery 2014; Statistical Solutions©)

Data Analyses Plan: We will select patients with low and moderate risk of PE and a normal chest radiograph. This selection strategy is designed to minimize "crossover" (randomized to VQ/no exposure, but go on to need a CTPA/exposure) (ACR Appropriateness Criteria© https://www.guideline.gov/popups/printView.aspx?id=35135, accessed 4/27/2016). Based published literature and our preliminary data, we conservatively anticipate that the crossover rate will be <5% using this selection strategy (see *Preliminary Data* and *Tables 3 and 4*). [49-52] Patients both the CTPA (exposure) and VQ (no exposure) groups will have the same post-test probabilities of PE and the risk of AKI (primary outcome) is not affected by the presence or absence of PE. For all analyses, patients will be considered in the groups to which they are randomly assigned. Statistical significance will be defined by the two-sided p-value <5% (SAS® v 9.1; SAS Institute Inc.).

Baseline Data Analyses: For each of two groups, we will be summarize continuous variables by group using descriptive statistics and categorical variables by frequency counts and percentages. Baseline clinical and demographic data will be compared between two groups to assess the effectiveness of the randomization. Dichotomous and ordinal variables will be examined using chi-square tests and continuous measures with Student's t-tests. Exploratory analysis will be performed to compute p-values which will be presented as an aid to evaluate the overall comparability of the two groups at baseline.

Missing Data Analysis: We anticipate a possible screening and randomization failures (5%)[49-52] and dropout (30%)[7,11,20,53,89] and have adjusted the sample size. It is very unlikely that the dropout mechanism will depend on the unobserved outcome and we will compare the baseline covariates between the dropout and non-dropout groups for substantial differences. Under circumstances where compromise of power may be compromised by missing values, we will use a multiple imputation procedure to make use of all relevant observed data and assume that the data are Missing At Random (MAR), using the SAS® MI and MIANALYZE procedures.

Primary Outcome Analysis: For our primary aim, we will test the following hypothesis:

$$H_0 : |\varepsilon| \geq \delta \quad \text{vs.} \quad H_a : |\varepsilon| < \delta; \text{where } \varepsilon = P_1 - P_2 \text{ and } \delta = 10\%$$

P_1 and P_2 are the true AKI rates in the CTPA and VQ groups, respectively.

We will reject the null hypothesis and the two groups, CTPA and VQ, will be considered equivalent if

$$\frac{\hat{P}_1 - \hat{P}_2 - \delta}{\sqrt{\hat{P}_1(1-\hat{P}_1)/n_1 + \hat{P}_2(1-\hat{P}_2)/n_2}} < -z_{0.05} \quad \text{and} \quad \frac{\hat{P}_1 - \hat{P}_2 + \delta}{\sqrt{\hat{P}_1(1-\hat{P}_1)/n_1 + \hat{P}_2(1-\hat{P}_2)/n_2}} > z_{0.05}$$

If we reject the hypothesis of equivalency, we will conduct an analysis for a superior trial. Hence, for comparison with the dichotomous primary outcome, that is, whether a subject develops AKI at the 2-7 day follow-up, a logistic regression model will be used. Group comparisons will be adjusted for baseline covariates. To validate the decision rule in classifying subjects into a low-risk group we will: 1) Measure the AKI rate in the low-risk group (AKIrisk Score <2) with a desired margin of error. We assumed the upper limit of the one-way 95% confidence interval to be <10%, based on preliminary data, and prior literature.[6,7] as such, we will compute the one-way 95% confidence interval using a Z test statistic; and 2) Compute sensitivity and specificity of the decision rule.

2.2 Secondary objectives
The secondary objectives of this study are to:

1) Validate the AKIRisk score, alone and in combination with acute-phase markers of renal dysfunction (Cystatin-C and/or NGAL), to inform imaging strategies and reduce the risk of AKI.
2) Compare the incidence of short, mid- and long-term AKI and subsequent health outcomes in patients exposed to iodinated contrast media and unexposed controls at 30-days and at 1-year.
3) Measure the 30-day and 1-year incidence of VTE and subsequent severe health outcomes including outcomes related to VTE and VTE treatment.

All secondary outcomes will be defined using composite outcomes and will be determined to be present or absent by the agreement of 2 of 3 blinded physician reviewers, using methods of adjudication successfully employed by the PI in comparable studies.[7,11,20,46,53,59] Briefly, physician reviewers will be provided with copies of the EMR and patient interview responses. Identifying information will be redacted, and, while the reviewer will have access to any creatinine values recorded in the EMR, they will not be provided with creatinine measurements performed for the study and not recorded in the EMR, nor will they be informed of the subject's status with regard to the primary outcome. Each reviewer will be asked to define each secondary outcome as present or absent, without knowledge of the other reviewers' determinations. In the event of a disagreement between the first and second reviewer, the determination of a third reviewer will be used to define the outcome. No reviewer will be made aware of their designation as the first, second or third reviewer.

Acute Kidney injury will be reported using defined using the Acute Kidney Injury Network (AKIN) definitions (stages 1-3). [90] KDIGO guidelines do recommends a more standard definition of AKI than for CIN.[38] While we do agree with this recommendation, in principle, we are planning a study aimed at changing imaging practices of physicians in specialties that are not as familiar with the. We do plan to measure and report AKIN 1-3 outcomes. We also plan the enrollment of a heterogeneous cohort of patients with renal function ranging from normal to significantly impaired and patients with a range of acute and chronic illnesses of varying severity, consistent with patients treated in the emergency care setting.

Venous Thromboembolism (VTE) including PE and/or DVT will be defined by the identification of one or more thrombus, requiring medical or surgical intervention, in the deep veins of the extremities or in the pulmonary vasculature as determined by ultrasonography, echocardiography, CT, MRI, VQ or on autopsy. We will also record and report severe outcomes secondary to VTE and treatment of VTE, including hemorrhage from anticoagulant treatment.

Complications of PE imaging will be defined for the first 24 hours after imaging, patients will be followed for one or more of the following recorded in the EMR, and requiring medical or surgical intervention: hypotension defined as a SBP ≤90 mmHg or ≥10% below baseline, dyspnea, acute pulmonary edema or hypervolemia, oral swelling, rash or puritis, abdominal pain, nausea or vomiting, altered mental status, or soft tissue contrast media or radio-isotope extravasation. The PI has previously published these methods of outcome determination.[53]

Severe Health Outcomes will be defined for each follow-up period (24 hours, 2-7 days, 30 days, and 1 year) as the combined outcome of death from any cause, renal failure, acute myocardial infarction, stroke, and/or one or more symptomatic complications of arterial-vascular disease, in any distribution, (cerebral, coronary, mesenteric, renal or peripheral) requiring surgical or medical therapy.[28] Renal failure will be defined by the AKIN 3 criteria: an increase in creatinine 3 times baseline, or a decrease in $eGFR_{SCr}$ ≥75%, or an absolute increase in creatinine to ≥4.0 mg/dL as a result of an increase of at least 0.5 mg/dL, or the need for renal replacement therapy.[90] The highest recorded creatinine recorded in the EMR during the follow-up period will be used to determine this outcome. Myocardial infarction will be defined as a cardiac catheterization, autopsy or cardiac imaging study demonstrating acute coronary thrombus or non-viable myocardium; or at least one measured troponin I above the 99th percentile and clinical findings consistent with ischemia; or diagnostic ECG findings including acute ST-T changes, new left bundle branch block, or new pathologic Q-waves.[96,97] Stroke will be defined as an acute, focal neurologic deficit with symptoms lasting longer than 24 hours and/or imaging or autopsy evidence of acute cerebral infarction. Finally, coronary or cerebrovascular events not meeting the criteria for acute myocardial infarction or stroke, including acute coronary syndromes and transient ischemic attack (TIA), are included within the definition of other arterial vascular events if these events required medical or surgical invention. The PI has successfully applied the same methods of outcome determination in a comparable study.[7,11,20]

Outcomes involving death will be classified by adjudicators as:1) Renal injury as a significant contributor defined as obvious evidence of renal failure defined by worsening azotemia with complications of renal failure including oliguria, pulmonary edema, hyperkalemia, pericardial effusion, or the need to initiate renal replacement therapy before death; 2) Death from VTE and/or hemorrhage requiring intervention following anticoagulant treatment for VTE; or 3) Unrelated to VTE or Renal injury. Death outcomes 1) and 2) may be identified concurrently.

Sample Size We will use a prospective validation study design for the previously derived decision rule (AKIrisk Score), classifying subjects into low AKI-risk group. We will recruit 100 subjects undergoing CTPA with an AKIrisk Score <2. Since the overall AKI rate in our patient population of interest is <10% (see *Preliminary Data*), the group of subjects with AKIrisk Score <2 will have much lower AKI rate. Assuming 5% AKI rate in this low risk group, the upper limit of one way 95% confidence interval will be ≤9.3% with a sample size of 100 (adjusted for dropout and screening failures).

Secondary Outcome Analysis: We will measure several secondary outcomes of which almost all are dichotomous (e.g. death, renal failure, stroke and/or other acute arterial vascular events). We will use a logistic regression model including the baseline covariates in the model. In case of rare events, we will use an exact logistic regression analysis. For the change in continuous outcomes, we will use ANCOVA model including the baseline covariates. Using similar analyses, we will compare baseline outcomes between enrolled subjects and subjects who will meet the inclusion criteria but decline participation in the study. Finally, we will compare outcomes of patients, relative to the AKIrisk Score, and we will compare outcomes and demographic data of those who enroll versus those who meet inclusion but decline participation to assess for possible bias induced by the informed consent process.[84]

3.0 Study Design

This is a prospective, cohort study of patients with low or moderate risk of PE (a pretest [pre-imaging] probability of PE ≤ 20%).

3.1 Number of Study Subjects

We will identify and enroll 2 groups of patients:

1) 100 patients undergoing CTPA with an estimated risk of CIN <10% (AKIrisk Score <2).
2) 600 patients with an AKIrisk Score ≥2, randomized to CTPA (exposure to iodinated contrast media) or VQ imaging (unexposed control).

3.2 Number of Study Sites

The study will be conducted at 5 emergency care sites: IUH Methodist Hospital (also provides emergency care services for IUH University Hospital), Eskenazi Health Hospital, IUH Ball Memorial Hospital, University of Untah, and Intermountain Healthcare.

3.3 Duration of Subject Participation

Patient involvement will last one year, inclusive of follow-up review of their medical records. The primary outcome of AKI consistent with CIN will be measured once between 2 and 7 days (≥48 hours and ≤168 hours) after enrollment PE imaging. Safety outcomes will be followed for occurrences up to 7 days after the enrollment PE imaging study. Secondary study outcomes will be assessed starting at 30-days and 1-year.

4. Study Population

4.1Subject Recruitment and Enrollment Strategy

The study is open to both genders, all races and ethnicities. This study will enroll women and minority patients. We expect approximately 60% women and 35-50% minority representation, and 1-3% of Hispanic/Latino origin. The Targeted/Planned Enrollment table was completed based on the PI's and co-investigator's (Kline) experience enrolling patients diagnosed with PE and in consideration of the preliminary data at the enrollment sites. We expect the proposed study enrollment demographics to mirror those of prior studies. Asians, Native Hawaiian or other Pacific Islanders are included at a <1% rate Targeted/Planned Enrollment Table because of their low prevalence in the local population, which mirrors National epidemiological studies of PE and a large sample of patients tested for PE from 12 emergency departments in the United States.[101,104] Patients who are incarcerated or institutionalized are not able to participate in the research activities including an initial interview, a follow-up blood draw and interviews, will be excluded. Patients who, for other reasons cannot provide written, informed consent, a next of kin or persons with power of attorney will consent on their behalf. This study will not enroll children or pregnant women. Physiologic differences unique to neonates, children, pregnant women (and fetuses) may have some important but unknown effects on the development of CIN. This study is not designed to measure these differences and we do not expect to enroll enough of these patients to specifically investigate these differences. Furthermore, while the overall risk of exposure to ionizing radiation is equivalent between CTPA and VQ, CTPA involves linear radiation applied across the thorax and upper abdomen, whereas with VQ, the nuclear isotope is administered parenterally. As a result, fetal exposure to ionizing radiation may be higher with VQ.

Patients will be enrolled in the emergency departments of five hospitals: 1. IUH Methodist Hospital (which also provides emergency care services at IUH University Hospital), 2. Eskenazi Health (formerly Wishard) Hospital, IUH Ball Memorial Hospital, University of Utah, and Intermountain Healthcare. Patients may also complete their imaging studies and, for patients hospitalized >48 hours, may complete their initial follow-up at IUH University Hospital. Examination of data for all emergency department patients who have had a CTPA scan ordered from the two enrollment sites over the past three years reveals mean age 49±16 years with 54% African American, 44% Caucasian, 0.8% Asian, 1% American Indian 1% report Hispanic Ethnicity, and 51% are females; payers include Medicare (22%), Medicaid (25%), Private or commercial insurance (19%) and self-pay (34%). The patients have a high burden of comorbidities, and approximately 65% of all patients are admitted to the hospital. These demographic data match up well with those published in the last three National Hospital Ambulatory Medical Care Surveys (NHAMCS)—a survey designed to collect data on the utilization and provision of ambulatory care services in hospital emergency and outpatient departments. Findings are based on a national sample of visits to the emergency departments and outpatient departments of non-institutional general and short-stay hospitals.[98-100] Additionally, the table below shows the demographic characteristics of a large sample of patients evaluated for possible PE in 12 emergency departments, not including any hospitals in Indianapolis.[101] The almost 2:1 predominance of women undergoing CTPA scanning from the emergency department setting has been shown repeatedly in the United States, and to a lesser extent, in Europe.[55,102]

Demographics of Patients Evaluated for Pulmonary Embolism in the Emergency Care Setting		
	12 Centers Not Including Indianapolis	Indianapolis

	n = 7940		n = 200
	n	% or Mean	% or Mean
Age		49±16	49±16
Female	5328	67%	65%
White	4541	57%	61%
Black	2704	34%	29%
Hispanic	482	6%	9%
Asian	74	1%	1%
Other Race	139	2%	<1%

Patients will be identified under IRB approved waiver of authorization of release of medical records for the purpose of research. Both sites have comprehensive patient flow and computer order entry systems with real-time order alert systems that will be used to identify patients (IUH Methodist and IUH University Hospitals: Cerner©, Kansas City, MO; Eskenazi Health Hospital: Epic Systems Corporation©, Verona, WI). Notably, the applicant's research team is facile with alert systems within the EMR. As demonstration of the current success of the patient-identification process, over 2,275 of patients undergoing imaging studies for PE have been screened for an active research trial of nitric oxide to treat PE (www.clinicaltrials.gov, protocol NCT01939301, conducted by Dr. Kline, a co-investigator on this proposal). The PI will leverage these existing alerts to identify potential study participants for the proposed study.

Following the first 3 months of enrollment, we plan to evaluate our enrollment process with administrative imaging logs (DORIS, Indiana University Health Department of Radiology) to evaluate potential bias in the enrollment protocol. Written, informed consent will be obtained from all study participants.

As a part of the informed consent process, participants will agree to have their creatinine and a urine dipstick measured at enrollment, and for investigators to draw and use blood and urine samples for purpose of research (to measure Cystatin-C and NGAL). Participants will also provide written informed consent to use blood and urine samples for measurement of biomarkers of AKI-risk in future work. Patients will also agree to return for a follow-up interview and have their creatinine measured between 2 and 7 days after enrollment, complete a telephone follow-up interview, and give permission to obtain their medical records to complete follow-up at 24 hours, 1 week, 30 days and 1 year.

The subject's EMR will be screened for initial inclusion and exclusion criteria. A study investigator or coordinator will approach the potentially eligible patients for consent. If not already documented in the EMR, the study coordinator will complete the PE PreTest Consult Score and AKIrisk Scores and determine eligibility. This process may involve the treating provider for input on the risk score results. If not already performed within 7 days, an order for a chest radiograph will be placed in conjunction with the clinical team, the study coordinator will also perform a bedside urine dipstick to identify glycosuria ≥ 250mg/dL (1+ or greater) for patients who have not already had a urinalysis performed within 24 hours. If the patient is eligible, the coordinator will obtain the patient's written informed consent, collect basic data, and may collect urine and blood samples.

The research associate or investigator will make every attempt to talk to the patient without distractions in or around the room. Where appropriate, the investigator will personally speak to family members in quiet family rooms. Informed consent forms will be signed at the point of care by the patient. The patient will be given adequate time to make a decision. The patient will be given a copy of the informed consent document.

4.2 Inclusion Criteria

1. Age≥18 years
2. CTPA ordered by the treating provider to evaluate PE.
3. Pre-test probability of PE ≤20% (defined using the PE Pretest Consult Score)
4. For randomization to CTPA or VQ imaging: Pre-imaging CIN risk ≥20% (AKIrisk Score ≥2 points)

- A lower-risk subset of 100 patients (AKIrisk Score <2) will be enrolled and followed. These patients will complete the CTPA as ordered by their provider (not randomized). Data from this lower-risk subset, along with high-risk patients randomized to CTPA will be used will be used to validate the AKIrisk Score, alone and in combination with NGAL and $eGFR_{CYS}$ (Study Aims 1 and 3).

4.3 Exclusion Criteria

1) History of pulmonary surgery or findings on chest-radiograph that may limit the accuracy of VQ imaging for the detection of PE including air-space disease occupying more than 50% of the lung field, significant mass, or pleural effusion of significant volume or associated with low-lobe air-space diasease.
2) Clinical instability or other condition preventing randomization to CTPA or VQ imaging.
3) Pregnancy or ≤48 hours post-partum.
4) Subject unavailability for reasonable follow-up including biological sample collection, creatinine measurement, and interview, such as an insecure residence, planned travel or absence, personal or professional obligations, incarceration, and/or other reason preventing follow-up, identified at enrollment.
5) Active renal replacement therapy (hemodialysis or peritoneal dialysis) within 30-days of enrollment or previous physician-directed plans to initiate dialysis within 30-days of the index visit.
6) Prior renal transplant or planned within 30-days of enrollment.
7) Intravascular contrast administration within 14 days prior to enrollment or planned within 7 days of enrollment.

4.4 Randomization

Subjects will be randomly assigned to either the CTPA group or the VQ group (1:1 ratio) using a computer generated randomization list with a block size of 4. Assignment will utilize REDCap (Research Electronic Data Capture, hosted by Indiana CTSI, https://redcap.uits.iu.edu/), a secure web-based application that will automate a separate, computer based randomization list for each enrollment site, generated by the biostatistician (Saha).To balance in the risk of PE, we will use the PE PreTest Consult Score as a stratification factor (a <10% risk group and a 10-20% risk group).

4.5 Moment of Enrollment

Enrollment occurs when the consent form is signed and dated, randomization is complete, and the subject completes the study-assigned PE imaging study.

5. Study Procedures

5.1 Main Measurements

Collection of blood and urine samples may be obtained around enrollment and the initial follow-up (2-7-days). We will collect blood and urine samples, using standard collection methods.

Enrollment Data Collection: The study coordinator will collect the following data: age; sex; race and ethnicity; vital signs; current medications and treatments (including anticoagulation and/or thrombolysis treatment for VTE); comorbid conditions (acute and chronic); the type and severity of prior adverse reactions to iodinated contrast media; physiologic indicators of acute disease (EKG findings of cor pulmonale, indications of right-heart strain and other echocardiography data, cardiac biomarkers including troponin and brain natriuretic peptide [BNP], and lactate); and literature-derived risk factors for CIN.[18,23,28,41,60-83] We will also record the type and volume of intravenous fluid administered 12 hours prior to and within 24 hours following the enrollment imaging study.

Baseline Creatinine Measurement If the study participant received a baseline creatinine measurement, documented in the EMR, within 24 hours of imaging around enrollment, this measurement will be used as the baseline measurement for our study. If not, we will measure a creatinine level from the blood sample collected at enrollment, if applicable.

Follow-up Creatinine Measurement The follow-up blood draw and creatinine measurement will be performed no sooner than 48 hours and no longer than 7 days (168 hours) following the enrollment imaging study using methodology established by the applicant.[7,11,20,89] At the time of enrollment, regardless of plans for discharge or

hospitalization, study participants will be scheduled for a return visit to their site of enrollment. The patient will receive a reminder card with the date, time, and location of their follow-up appointment and a contact phone number for the study coordinator. If the patient remains hospitalized 48 hours or more following the enrollment imaging study, we will record the highest creatinine value measured during the specified follow-up time of 2-7 days, or if needed, complete the creatinine measurement. If the patient is hospitalized, but discharged prior to the follow-up period, follow-up will be completed as previously scheduled. A $50 dollar stipend will be provided for patients that complete the return appointment as reimbursement for travel costs and time.

Telephone and Medical Record Follow-up The methods planned for follow-up were developed in part by the PI and her co-investigator (Kline), have been previously published,[89] and successfully used to complete follow-up for a study of CIN incidence and subsequent outcomes.[7,11,20,53] The methods planned for follow-up were developed in part by the PI and her co-investigator (Kline), have been previously published,[89] and successfully used to complete follow-up for a study of CIN incidence and subsequent outcomes.[7,11,20,53] Follow-up interview will also occur during the 2-7 day follow-up appointment. For patients who did not complete the follow-up visit, we will attempt to contact the patient by telephone and/or email starting at 7-days following enrollment (to identify events occurring within 7 days of enrollment). A review of the EMR will also be performed for outcomes occurring within 24-hours, 7-days, within 30-days and within 1-year. A Social Security Death Index search will be performed for all patients that could not be contacted by telephone or email and for whom survival could not be confirmed by the medical record. In the event of a death, we will attempt to obtain a copy of the death certificate, if available.

5.2 Safety measurements

The study manager will monitor for occurrences of one or more of the following events occuirng within 7 days (168 hours) of the enrollment PE imaging study:

1) Time to treatment of PE >8 hours defined as the time from study enrollment until initiation of anticoagulant therapy for PE.
2) Complications of PE imaging defined as one or more of the following occurring within 24 hours of the enrollment imaging study and requiring medical or surgical intervention: hypotension, difficulty breathing, acute pulmonary edema or hypervolemia, oral swelling, rash or puritis, abdominal pain, nausea or vomiting, altered mental status, or soft tissue contrast media or radio-isotope extravasation.
3) Severe health outcomes defined as one or more of the following occurring within 168 hours of the enrollment imaging study: AKI (Acute Kidney Injury Network [AKIN] 1-3); Death (any cause), renal failure, or one or more of the following requiring medical or surgical intervention: acute myocardial infarction, stroke and/or other acute arterial vascular event, in any anatomic distribution, requiring medical or surgical intervention; death with renal injury as a significant contributor defined as obvious evidence of renal failure defined by worsening azotemia with complications of renal failure including oliguria, pulmonary edema, hyperkalemia, pericardial effusion, or the need to initiate renal replacement therapy before death; identification of a venous thromboembolism (VTE, PE and/or DVT) requiring medical or surgical intervention; death from VTE and/or hemorrhage requiring medical or surgical intervention as a result of treatment for VTE.

5.3 Study schedule and benchmarks

Study Events Schedule						
Procedure	**Screening/ Enrollment**	**24 Hours after PE Imaging**	**≥ 48 hours and ≤168 hours**	**7-Day Follow-up**	**30-Day Follow-up**	**1-Year Follow-Up**

			after PE imaging			
Inclusion/Exclusion Review	X					
Informed Consent	X					
Chest Radiograph	X		X			
Urine Sample	X		X			
Blood Sample/Creatinine	X		X			
Interview			X	X (If return visit not completed)		
EMR Review	X	X	X	X	X	X
Assess Primary Outcome			X	X		
Assess Secondary Outcomes		X	X	X	X	X
Asses SAEs		X	X	X		

6.0 Safety Assessment and Reporting

The study coordinators will also communicate closely with the clinical team, inform them of the PE imaging randomization assignment, and assist the clinical team to coordinate the completion of the PE imaging. The study coordinator will notify the treating provider of any conditions that exclude the patient from participation in this study. A study physician will be available by telephone during patient enrollment and the completion of PE imaging. The flowchart shown in appendix 1. describes the study procedures including randomization, assessment of outcomes, and PE imaging completion, including the process for crossover from the VQ arm to CTPA. Patients with suspected DVT will also undergo lower extremity ultrasound (US), at the discretion of the treating provider, as will patients with an intermediate risk VQ. Thus, only patientswho, after pre-enrollment screening for non-high risk of PE, appropriateness for VQ imaging, have an intermediate risk VQ study and a negative DVT US, will require crossover to CTPA to exclude PE.

Patients who develop CIN, based on the study definition and follow-up creatinine measurement, will receive a telephone call notifying them of this result. If the patient cannot be reached by telephone, we will also send a letter (paper mail, and if provided, email) informing them of their creatinine measurement. The same notification letter will provide instructions to seek follow-up care with either their primary care physician, or for patients without a primary care physician, with instructions to follow-up in the emergency department.

6.1 Criteria for Discontinuation of Study

If we find that lower limit of 95% confidence interval of the difference in rate of AKI is greater than 15% between groups, we plan to discontinue the study. This will be assessed annually.

6.2 Adverse Events

6.2.1 Definitions

An **adverse event** (AE) is any undesirable medical occurrence or untoward deviation in health from baseline. A **serious adverse event** (SAE) will be defined in accordance with ICH-GCP guidelines (any unexpected illness or injury that poses a threat to life or body function and causes medical or surgical intervention or prolongation of hospitalization). An **unanticipated adverse event** is one that is not identified in nature, severity, or frequency in the current protocol and informed consent document. A **related adverse event** or **adverse effect** is one that is definitely or probably a result of participation in the study (likely would not have occurred as part of standard care).

6.2.2 Investigator Records

Records and documents pertaining to the conduct of this study, CRF and consent forms will be maintained by the PI for 2 years after the investigation is discontinued. The study binder will contain information including IRB approval letters, documentation of GCP training, human subjects research ethics training certificates, curriculum vitae, and correspondence.

6.2.3 Follow-up Procedure

Safety assessments will consist of monitoring, using the methods previously defined, and reporting serious adverse events (SAEs) that could be considered unanticipated and related to study participation in accordance with CFR 312.32 (IND Safety Reports). CRFs will be inspected periodically and compare them with certified source documents. In addition to the original medical record, the study will employ a data collection template as a source document. This form contains the data fields that historically have been difficult to abstract from the medical record.

6.2.4 Investigator Reports

All serious adverse events (SAEs), related or unrelated to the study, will be reported to the PI and project manager by scanning a copy of the IRB SAE reporting form and attaching to an email addressed to the project manager and PI.

All SAEs occurring within 168 hours of the enrollment imaging study, whether reported by the patient, or discovered from the medical record will be reported. Each SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria, and, if applicable, suspected relationship to study participation. In general, these relationships will be categorized as likely, possible, unlikely and not related.

Adverse events (SAEs or AEs) that are known to occur with patients who are evaluated for PE with either CTPA or VQ, and, if identified on imaging, with a VTE (PE and/ or its precursor DVT), will be considered to be anticipated and excluded from reporting to the NIH (but not from internal analysis) unless determined to be serious, unanticipated and related. This information will be assessed quarterly by the Principal Investigator.

The following signs, symptoms, observations and events are frequently observed in association with CTPA and VQ imaging, and with PE and/or DVT, treatment for VTE, or other cardiopulmonary emergencies that will be diagnosed and are exempted from regulatory reporting unless serious, unanticipated and related to the study: hypotension, dyspnea, acute pulmonary edema or hypervolemia, oral swelling, rash or puritis, abdominal pain, nausea or vomiting, altered mental status, or soft tissue injury from contrast media or radio-isotope extravasation, chest pain, fever, hypoxemia, rapid pulse, rapid respiratory rate, dizziness, syncope, altered mental status, seizure, confusion, anxiety, tingling sensations, numbness or pain of limbs, generalized weakness, exertional intolerance, hemoptysis, anorexia, nausea, abdominal pain, back pain, constipation, vomiting, congestive heart failure, angina pectoris, pneumonia, skin infection, limb swelling, cancer, surgery not related to treatment of VTE or hemorrhage, electrocardiography abnormalities (atrial arrhythmias, right bundle branch block, and ST and T wave changes), pulmonary hypertension, pulmonary infiltrate, pleural effusion, cardiomegaly, need for oxygen therapy, need for physical or occupational therapy, and hemorrhage associated with anticoagulant therapy.

Diagnosis vs. Signs and Symptoms: If known at the time of reporting, a diagnosis will be reported rather than individual signs and symptoms. However, if a constellation of signs or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it will not be reported as an SAE. Purely descriptive terms will not be used as the basis of an SAE (e.g., “chest pain, etiology unknown”). If a diagnosis is subsequently established, it will be reported as follow-up information.

Deaths: All deaths that occur during within 7 days, regardless of attribution, will be reported, if required by IRB, using available information regarding causation and relationship.

Preexisting Medical Conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions will be reported as medical and surgical history. A preexisting medical condition will be re-

assessed throughout the trial and reported as an SAE only if the frequency, severity, or character of the condition worsens during the study to the point where it requires intervention to prevent loss of life, limb or organ function.

Hospitalizations for Medical or Surgical Procedures: Any AE that results in hospitalization or prolonged hospitalization will be documented and reported as a SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, will be reported as the SAE. At follow-up, if the patient indicates he or she had a hospitalization (defined as non-observational stay >24 hours in an acute care facility), the study coordinator will obtain a copy of the discharge summary for each hospitalization and will report, verbatim, on the CRF the discharge diagnoses listed.

6.2.5 Expedited Safety Reports

All serious adverse events that are unanticipated AND related to study participation will be reported to the DSMB within 24 hours of discovery and shall include the following information:

i. Nature of adverse effect
ii. Statement as to why it is considered unanticipated
iii. Statement as to the degree to which it is considered study related, and why
iv. Results of any diagnostic tests that were performed
v. Description of any treatment implemented
vi. Statement of subject's current clinical status
vii. Investigator's signature and date

The investigator shall supply a copy of the report for adverse events that are unanticipated AND study related to the reviewing IRB.

6.3 Data Safety Monitoring Board

Charter, Data and Safety (Observational Study) Monitoring Board for the Randomized trial of Ventilation-Perfusion Scintigraphy versus Computed Tomography of the Pulmonary Arteries for Acute Kidney Injury Incidence

Revision date: February 20, 2018

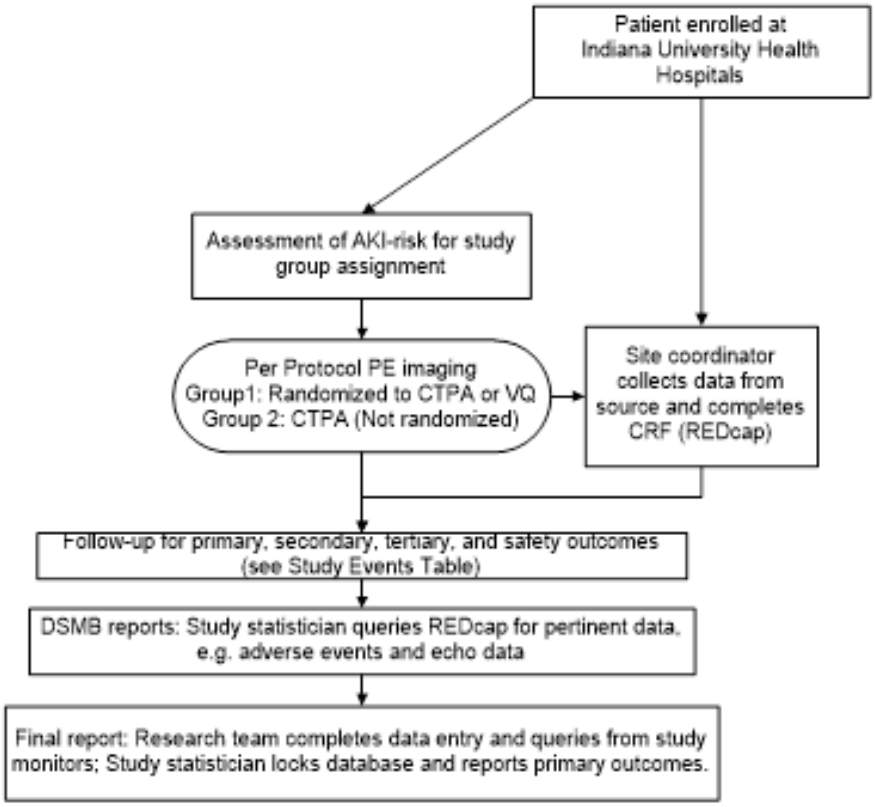
1. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study and carrying out the Safety Plan.

The DSMB is an independent group that provides recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety
- Notification of and referral for abnormal findings

2. Organization and Interactions



This study will be initiated at 2 emergency care sites (three hospitals) in Indianapolis, IN, Eskenazi, University, and Methodist hospitals (collectively abbreviated as IU, Alice M. Mitchell, PI). Meetings will be scheduled by the study team.

Communication with DSMB members will be primarily through the study team. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

3. DSMB Members and NHLBI Program Staff

DSMB members and their expertise [pending]. NHLBI Program Staff involved in the study [pending]. Consistent with NHLBI policy, each DSMB will choose an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

4. Scheduling, Timing, and Organization of Meetings

DSMB meetings will be conducted by telephone conference. Meetings will occur prior to study initiation, annually during the 4 year period of the project, and will be convened as needed for SAEs that are unanticipated and study related. The purpose of the first meeting is to select an Executive Secretary (ES), review and discuss this Charter, to provide an overview of study activities, and to review and make recommendations about the protocol. Enrollment in a study cannot begin until the DSMB's recommends approval and IRB approval of any changes to the protocol has been obtained.

The agenda for DSMB meetings and calls may be drafted by the study team in consultation with NHLBI staff. The ES will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials

should be distributed by the DCC one week before each meeting or call. The NHLBI program official should be informed of upcoming board meetings at least 1-2 weeks in advance, and receive the appropriate meeting materials at the same time as the board members.

Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last meeting. If a new conflict is reported, the Chair and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point.

It is expected that all DSMB members will attend every meeting either in person or by conference call. However, it is recognized that this may not always be possible. Therefore, the DSMB may wish to discuss whether establishing a quorum for voting is desirable. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

5. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the study manager, study investigators and NHLBI staff as appropriate, with time for discussion.

- During the **closed sessions**, the DSMB, and NHLBI staff will discuss confidential data from the study, including information on efficacy and safety by treatment arm. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

The DSMB may elect to hold an **executive session** in which only the DSMB members and Executive Secretary are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR)** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert)

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators, the DCC, and NHLBI to ask questions to clarify the recommendations. The meeting is then adjourned.

6. Reports of DSMB Deliberations

- Formal minutes/summaries: The ES is responsible for the accuracy and transmission of the formal DSMB minutes or summary within 30 days of the meeting or call. These minutes are subject to FOIA requests and are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the

recommendations from the current meeting. These minutes will be reviewed by key study personnel, and the DCC before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Subsequently, the minutes and materials are sent back to the DCC and the relevant investigators, for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.

- DSMB Recommendations: The lead investigators must arrange for a summary of board recommendations to be sent to each participating IRB. The recommendations are also sent to the study manager, NHLBI, and the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, NHLBI staff, in collaboration with the study manager, will prepare an action plan outlining the steps required to implement the recommendations.

7. Reports to the DSMB

For each meeting, the study manger with input from NHLBI staff, will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

8. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons.

The DSMB can choose to recommend stopping the trial early for evidence of HARM or FUTILITY.
A recommendation to stop for HARM would occur if an interim analysis showed strong evidence that the rate of delayed or missed cardiopulmonary SAEs is excessive in the interventional group. The final decision for stopping criteria will be made by the DSMB under advice by its lead statistician. As a general rule, it will be recommended that the DSMB biostatistician use the Lan and DeMets alpha-spending approach to early stopping, a generalization of the O'Brien-Fleming stopping rule adapted to interim analyses where the cumulative sample size is not known until the time of analysis. Briefly, the strategy will require extremely strong evidence of harm (or, equivalently, a very large critical value) at early analyses before making a recommendation to stop the trial. As more outcomes accrue, the stopping boundary will decrease, finally approaching the traditional value corresponding to a p-value of 0.05.

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Appendix 1. Flowchart of study events including study assignment of PE imaging with provision for crossover from VQ imaging to CTPA