Investigator Studies Program
Review Committee (MISP-RC)
IIS Clinical Concept Form

All fields are required, an incomplete form will be returned to the submitter. If a field is not completed, please note the reason.

Proposed Study Title	
Study Title:	Unmasking and unravelling of a silent killer: early detection of CTEPH
Document date	10-06-2016
Clinical Trial number	NCT03083093
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Study Information	
Indication	Pulmonary embolism / chronic thromboembolic pulmonary hypertension
Phase:	n.a.
Number of Subjects:	100 patients

Background and Rationale

- **Provide background on unanswered question(s) the study is attempting to answer (do not exceed one page)**

The ultimate consequence of hemodynamic compromise and persistent pulmonary perfusion defects after acute PE is chronic thromboembolic pulmonary hypertension (CTEPH), which is a lethal condition unless a timely diagnosis is followed by adequate treatment [1-5]. The exact incidence of CTEPH after PE is estimated to be 3.5-5.5% in patients without major cardiovascular of malignant comorbidity, within the first 2 years after the PE diagnosis [1-7]. Its pathophysiology has not been fully elucidated yet, although it has been established that the increased arterial resistance is caused by chronic obstruction of pulmonary arterial vessels by organised thromboembolic material as well as from vascular remodelling in small unobstructed vessels [2,3] CTEPH is the only potentially curable cause of pulmonary hypertension. Pulmonary endarterectomy (PEA) is the surgical procedure which removes the obstructing thromboembolic material, resulting in significant improvements and in many cases normalisation in pulmonary artery pressure and right ventricular function [1-3]. Early diagnosis of CTEPH is essential, since especially when detected at an early stage, CTEPH may be cured by pulmonary endarterectomy while delay in diagnosis may be associated with irreversible secondary pulmonary vascular remodelling and right heart failure, leading to worse prognosis, higher perioperative mortality and inoperable disease stages [1-8].

Early CTEPH diagnosis, however, has proven to be a major clinical challenge. First, there are no specific signs or symptoms of CTEPH and patients may remain asymptomatic for months to years although clinically significant pulmonary hypertension (PH) is already present [1,3]. On the other hand, 50% of patients report persistent dyspnea until years after acute PE, a symptom that may point to CTEPH but in most patients is due to deconditioning, death-space ventilation due to persistent thrombi or other cardiopulmonary comorbidities, and not to CTEPH [9]. Second, the exact incidence of CTEPH is unknown. Third, until now, no validated cost-effective screening tool is available, and the timing of screening is unknown. For instance, previous studies have shown that subjecting all patients who survived acute PE to transthoracic echocardiography, which is the recommended screening tool for suspected PH, has a low diagnostic yield, causes an excess of false positive findings that warrant additional diagnostic tests and is therefore not cost-effective [6,16]. Given these uncertainties, international guidelines do not provide a clear recommendation on the frequency and duration of medical follow-up after acute PE and even recommend against specific screening for CTEPH [6,7] Consequently, it has been established that the majority of CTEPH diagnoses nowadays still have a diagnostic delay 1.5 years, and in day-to-day clinical practice, many patients with a prior history of PE and non-specific cardiopulmonary symptoms are subjected to unstandardized and inefficient diagnostic tests [4,9].

While CTPA is the investigation of choice for the diagnosis of acute PE, planar V/Q lung scan remains the main imaging modality for CTEPH with a sensitivity and specificity of up to 97% [6]. Multidetector CTPA has nonetheless become an established imaging modality for confirming CTEPH although this investigation alone cannot exclude the disease [7,10]. CTPA characteristics of CTEPH include (calcified) eccentric wall-adherent filling defects, stenosis or obstruction (webs and bands) of pulmonary arteries with post-stenotic dilatation, dilatation of the pulmonary artery, right ventricular hypertrophy/dilatation, systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post-obstructive vessels) and mosaic lung perfusion pattern due to locally decreased perfusion [7,10,11]. Notably, most of these characteristics may also be found in patients with acute PE. Especially the aspect of the thrombus and the presence of webs and bands may be helpful in differentiating CTEPH from acute PE with acute right ventricular overload (**Figure 1**).

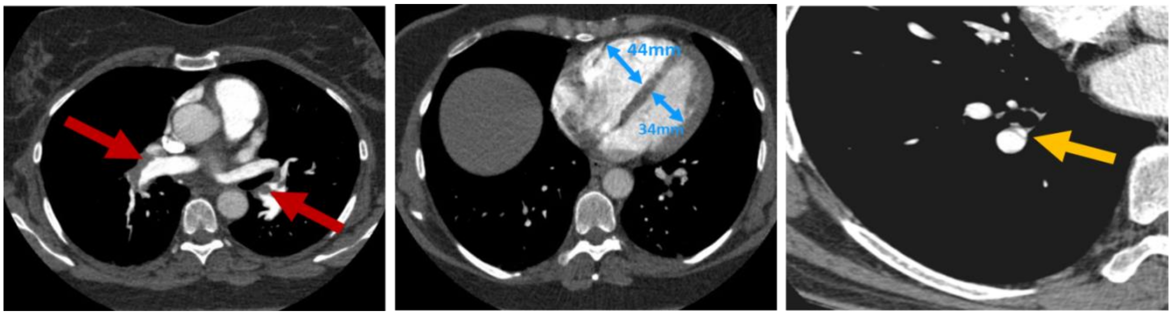

Figure 1: CTPA clearly visualizing large central blood clots in the pulmonary artery (left panel, red arrow) and right ventricular overload (middle panel, blue arrows) which may indicate both acute PE as well as CTEPH; Same CTPA with a very subtle indication of CTEPH by demonstrating an intraluminal web (right panel, yellow arrow)

Increasing evidence supports our hypothesis that in many cases CTEPH is misclassified as acute PE. As stated above, this hypothesis is based on the observations that 1) 1 to 2 in 4 CTEPH patients do not have a clear history of PE or DVT, 2) the pathophysiological mechanism of the transition of acute to chronic PE is unknown, 3) most thrombophilic conditions are not associated with CTEPH and 4) initial echocardiography and CT data at the time of an index PE suggest that a majority of patients who are later diagnosed with CTEPH, already had radiological signs of CTEPH at the time of the index PE diagnosis [1-3,7,12]. In clinical practice, radiologists who interpret CTPAs performed for diagnosing or ruling out acute PE are primarily focused on the diagnosis of acute PE and not on small subtle radiological patterns of CTEPH, although these may be present.

At the division of Image processing (LKEB) of the LUMC, prototype software has been developed to automatically quantify the pulmonary vasculature from CT images. With this innovative CT analysis method, the vascular tree is detected by so-called "vesselness"-filtering and "graph cuts" [13-15], and subsequently the architecture of this vascular tree is quantified by measuring the diameter of each vessel segment and calculating the frequency of occurrence of each vessel calibre (**Figure 2**).

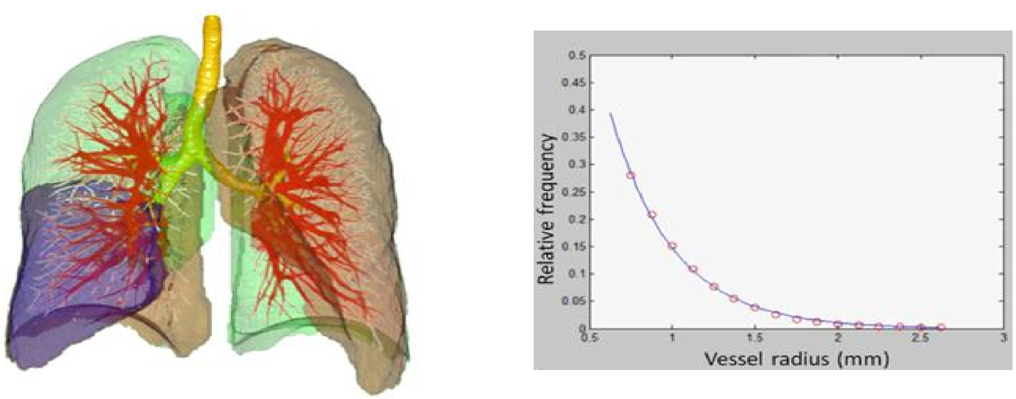

Figure 2: Pulmonary vasculature quantification: analyses of pulmonary vasculature with distribution of vascular calibre.

Since the pulmonary vasculature resembles a fractal, the fractal dimension can be calculated from this frequency distribution to describe its shape. This fractal-based imaging biomarker can be used to detect vascular changes in CTEPH, since the proportion of detected small and large vessels and therefore the fractal dimension will change. Hence, this technique may help differentiating CTEPH from acute PE on standard CTPA images.

Objectives

- **List the objectives to correspond directly with the listed hypotheses:**

Primary objective

To identify the accuracy of routine CTPA for the distinction of CTEPH from acute PE.

Secondary objectives

- To further develop the technique of automatic quantification of the pulmonary vasculature on CT scans, and correlate this fractal-based imaging biomarker to clinical features (CTEPH or not).
- To study the incremental value of NT-proBNP, troponin, ECG reading and the CTEPH prediction rule [16] to the diagnostic criteria of the CT scan that are derived in the primary analysis.
- To study the cost-effectiveness of additional extensive screening of CTPA images for the identified criteria for CTEPH.

Hypothesis

- **List the clinical Hypotheses in order of priority:**

1. More careful reading (than the current standard) of standard CTPA performed in the clinical work-up of suspected PE will differentiate patients with acute PE from those with more chronic or acute on chronic PE, which could be an early sign of CTEPH.
2. We further hypothesize that the novel imaging processing technique of “automatic quantification of the pulmonary vasculature” will greatly aid in differentiating acute PE from CTEPH. Furthermore, with this technique targeted, early and efficient/cost-effective screening for CTEPH may become possible.

Study Design/Clinical Plan

- **Provide a concise overview stating the type of experimental design**

For the first part of the study, we will study 50 consecutive patients diagnosed with CTEPH after an initial episode of acute PE and referred to the VUmc (period 2016-2018), as well as 50 patients diagnosed with acute PE in the LUMC in whom CTEPH was ruled out 2 years after the PE diagnosis by sequential echocardiography as part of standard care, matched on the RV/LV ratio of the patients who developed CTEPH.

Three experienced thorax radiologists with specific expertise on acute PE and CTEPH from LUMC (Dr. LJM Kroft), VUmc (Dr. L Meijboom) and AMC (Dr. LFM Beenen) will blindly assess the index CTPAs of the study population. The CTPA scans must be made on a 32-row detector (or more advanced) contemporary CT machines. The patients are matched on RV/LV ratio to force the radiologists to focus on the subtle aspects of the thrombi and the presence of webs and bands in the pulmonary arteries. In addition to the binominal judgement whether CTEPH signs are already present (or not), the presence of the standardised items will be scored by all 3 readers independently.
After the first 20 scan assessments by all three reviewers, an evaluation will be performed to check for logistical or other

issues that need to be solved before the final 80 scans will be distributed. If the 2 patient groups are successfully identified, the relevant diagnostic criteria that allow for this distinction will be summarized in a practical protocol.

For the evaluation of health economics, which will be supervised by an expert in this particular field, the mean time for the additional CTPA reading by the experts will be measured. In addition, using standard models and available data, the current diagnostic delay of CTEPH diagnosis and the associated costs and effects on quality of life will be assessed from the literature.

The final part of the study focuses on the further development of software that qualifies the functional pulmonary vasculature. In order to make the imaging biomarker of automatic quantification of the pulmonary vasculature more sensitive and specific, additional research is needed. This additional image analysis would include the distinction between the arterial and venous tree and quantifying their separate contribution to the fractal dimension. The segmentation of the vascular trees could also form the basis for a more detailed detection and local quantification of the acute PE and CTEPH-specific patterns, like vascular webs and abrupt changes in vascular dimensions. With every further step of software development, the specificity and sensitivity of the imaging biomarkers for specific vascular pulmonary diseases will be tested based on available scans form the clinics. After the technique of automatic quantification of the pulmonary vasculature on CT scans has been sufficiently developed (sensitivity and specificity of distinction between acute PE and established CTEPH both >85%), all CT scans in the derivation and validation set of the radiological criteria described above will be analysed accordingly to assess for clinical correlation to compare the diagnostic accuracy of the software with that of the expert radiologists (and the incremental value of both).

Treatment

- **List the clinical dosage/dosage form, route, and dose regimen:**

Treatment of the patients with acute PE and those with identified CTEPH will be according to international standards, and are not part of the study protocol.

Collateral Research

- **Include biomarkers, PK, etc.**

In addition to the primary endpoints, we will test the incremental value of NT-proBNP, troponin, ECG reading and our CTEPH prediction rule [16] to the diagnostic criteria of the CT scan that are derived in the primary analysis. Specifically, we will evaluate an innovative (automated) method for ECG reading for determination of the electric vector and estimation of the probability of right ventricular overload [17]. This 3-dimensional ECG-vector cardiogram (VCG) analysis will likely significantly improve the diagnostic value of ECGs for CTEPH when compared to the current manual ECG assessment. The main diagnostic improvement will be for patients with very early stages of CTEPH because even a small increase in pulmonary artery pressure will result in right ventricular pressure overload that is associated with subtle but clearly measurable changes in the electrocardiographically derived ventricular gradient as expressed by the electrocardiographic vector.

Statistical Plans

- **Include justification for clinical sample size and primary hypothesis testing:**

For the first part of the study, all three readers will independently assess the CTPAs. The final diagnosis for each arm of interest based on an aggregate reading of the CTPA images (acute PE or CTEPH with/without (sub)-acute PE) will be based on a majority rule. The sensitivity of CTPA is determined by calculating the proportion of scans that are read as "positive for the CTEPH specific radiological pattern” in patients with confirmed CTEPH and the specificity is determined by calculating the proportion of scans that are read as "negative for the CTEPH specific radiological pattern" in patients without CTEPH. The corresponding exact 95% confidence intervals for each of the point estimates will be calculated. In addition to these estimates, sensitivity and specificity estimates with corresponding 95% confidence intervals will be calculated for the initial independent assessment of each of the three readers participating. For the interobserver agreement between the reviewers a kappa statistic will be assessed. According to established criteria, a kappa score above 0.8 is considered excellent reliability, a score between 0.6 and 0.8 is considered good reliability, a score between 0.4 and 0.6 is considered moderate reliability and a score below 0.4 is considered poor reliability.

If the sensitivity of the CTPA is >90% with at least good interobserver agreement, we will conclude CTEPH may be excluded based on CTPA images. If the specificity of the CTPA is >90% with at least good interobserver agreement, we will conclude that the radiological pattern of CTEPH on CTPA performed to diagnose acute PE is highly predictive of a future CTEPH diagnosis and thus relevant to report and translate to the further diagnostic and therapeutic management of the patient. We will translate our findings in a set of diagnostic criteria, which should be validated in a future prospective study.

A sample size of 50 patients in each of 2 study groups was chosen because with this sample size and an expected specificity of greater than 90%, the 95% confidence intervals on the point estimates would have a bandwidth of approximately ±15%, ensuring that the point estimate was sufficiently accurate to make decisions about the appropriateness and safety of the proposed validation study.

The economic evaluation will include a study-based cost-effectiveness analysis (CEA) and a model-based cost-utility analysis (CUA).Both analyses will use net-benefit analysis, comparing the additional diagnostic test (extensive reading of the CT’s for presence of subtle signs of CTEPH on top of standard acute PE reading) to a strategy without this test. The CEA will be performed from a short-term healthcare perspective, estimating additional diagnostic costs per additional early CTEPH diagnosis. The CUA will be performed from a long-term societal perspective, estimating costs per quality-adjusted life year (QALY). In the CUA, the estimated diagnostic performance will be extrapolated to treatment decisions and patient outcome, using a Markov model to estimate the impact on health risks, survival, QALYs, health care and productivity costs.

For the software developing part of the study, no specific statistical tests are required. The accuracy of the final mathematical model will be compared with the accuracy of the manual reading of the CT’s by the panel of expert radiologist by receiver operating characteristic analysis, the incremental value of both by reclassification analysis.

REFERENCES

1) Kim NH et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013:D92-D99; 2) Lang IM et al. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013;41:462-468; 3) Lang IM et al. Update on chronic thromboembolic pulmonary hypertension. Circulation 2014;130:508-518; 4) Pepke-Zaba J et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973-1981; 5) Klok FA et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med 2010;181:501-506; 6) Konstantinides SV et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-3069k; 7) Galiè N et al. "2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension. Eur Respir J 2015;46:1855-6; 8) Lang IM et al. Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension. A case-control study. Thromb Haemost 2013;110:83-91; 9) Klok FA et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010;104:1744-1749; 10) Tunariu N et al. Ventilation-perfusion scintigraphy Is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680–684; 11) Doğan H et al. The role of computed tomography in the diagnosis of acute and chronic pulmonary embolism. Diagn Interv Radiol 2015;21:307-316; 12) Guérin L et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Haemost 2014;112:598-605; 13) Xiao C et al. Transactions on Image Processing 2013;22:174-88; 14) Xiao C et al. A strain energy filter for 3D vessel enhancement with application to pulmonary CT images. Med Image Anal 2011;15:112-24; 15) Zhai Z et al. International Society for Optics and Photonics; 2016, accepted for publication; 16) Klok FA et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016;14:121-8; 17) Kamphuis VP et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. J Electrocardiol 2014;47:175-82.

Budget Summary • Please be sure to complete budget template (excel document)	
Total Amount Requested: (Include overhead)	**Total amount €430k** *Personal costs* - 2 years PhD student (1.0FTE): €150k - 1 year Post-doc (1.0FTE): €100k *Material costs* - 100x CT scans (including blinding, distribution and post-hoc analysis by 3 independent radiologists): €80k - 100x Biomarkers (inclusive storage; NT-proBNP and Troponin): €20k - 100x ECG (including post hoc vector analysis): €20k - Software/Hardware for pulmonary vasculature quantification development: €50k *Other costs* - IRB costs: €1k - Publication costs: €3k - Travel costs scientific meetings PhD student and Post-doc: €6k
Additional sources of funding required? (Yes/No) If Yes, please be specific.	No
Timelines and Study Plans	
Number of Sites:	3
Site Names:	LUMC Leiden, the Netherlands VUmc, Amsterdam, the Netherlands AMC, Amsterdam, the Netherlands
Study Start Date:	1-1-2017
Study End Date:	1-1-2019
Number of Subjects:	100
First Patient In Date:	N.A.
Last Patient Out Date:	N.A.
Enrollment Period in Months:	2 years

Publication Plan	
Where are you planning to submit for publication? (journals, etc):	We aim to extract multiple publications from this project, which will be submitted to top ranked cardiology/pulmonology oriented journals, such as Circulation, Eur Heart J, Eur Resp J or Am J Resp Crit Care.
Are you planning to present your data at a scientific meeting?	**We will submit the abstract to the ESC annual meetings and/or ERS annual meetings**
Please list your target date for submission of publication.	1-6-2019
Drug Supply Information	
Drug Supplies Required (Yes/No)?	No
List Drug Supplies and Amount Required:	Drug Name: NA Amount: NA
List Drug Supplies and Amount Required:	Drug Name: NA Amount: NA
Placebo Required (Yes/No)?	No
Additional Sources of Drug Supply (Yes/No). If Yes, please specify	No