**Safety and efficiency of the YEARS algorithm versus computed tomography pulmonary angiography alone for suspected pulmonary embolism in patients with malignancy**

* **the Hydra study -**

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# Study synopsis

|  |  |
| --- | --- |
| Title | Safety and efficiency of the YEARS algorithm versus computed tomography pulmonary angiography alone for suspected pulmonary embolism in patients with malignancy |
| Short title | Hydra Study |
| Dutch title | Veiligheid en efficiëntie van het YEARS algoritme versus CT pulmonalis angiografie (CTPA) voor klinische verdachte longembolie bij patiënten met een maligniteit |
| Sponsor trial code | P18.xxx |
| NTR code | NTRxxxx |
| ABR research file number | NLxxxxx |
| Background | Recently, the YEARS-algorithm was demonstrated to be a safe and efficient diagnostic strategy for patients with clinically suspected pulmonary embolism (PE). It is recognized that diagnostic algorithms for pulmonary embolism (PE) may not be as effective and safe in patients with malignancy, due to the low specificity of D-dimer test in that setting. A diagnostic algorithm that could safely rule out PE in patients with malignancy without performing computed tomography pulmonary angiography (CTPA) could nonetheless improve patient care. |
| Primary objective | To prospectively validate the safety and efficiency of management according to the YEARS algorithm to safely rule out clinically suspected PE in patients with active malignancy to be compared with ‘standard’ management by CTPA alone in a randomized study. |
| Secondary objectives | To evaluate the occurrence (timing, location and severity) of recurrent symptomatic VTE during follow-up in both study arms in order to better differentiate between missed PE diagnoses and new onset VTE  To compare differences in the rate of isolated sub-segmental PE, defined as CTPA demonstrating an intraluminal filling defect in a sub-segmental artery with no filling defect visualized at more proximal artery levels, in both study arms  To assess the occurrence of incidental VTE, defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism during follow up in both study arms  To evaluate usage and safety of antithrombotic treatment in both study groups  To evaluate practice patterns of anticoagulation therapy during end-of-life care in terminal ill patients with cancer. |
| Study design | The Hydra-study will be a randomized controlled, multicenter international trial with a non-inferiority analysis for the main safety outcome (rate of 3-month VTE); if non-inferiority has been demonstrated at secondary stage a superiority analysis for the efficiency judgment criterion (rate of unnecessary CTPA) will be performed. |
| Study population | Consecutive patients with clinically suspected PE and active malignancy are eligible for inclusion. |
| Number of subjects | 1566 |
| Primary endpoints | (recurrent) PE, deep vein thrombosis (DVT), mortality |
| Secondary endpoints | Number of performed CTPA |
| Study duration and planning | The total duration of this study is expected to be 30 months. Ethics approval in the primary research center is aimed to be achieved by first quarter of 2019 and by April 2019 in the participating centers. Subject recruitment is planned to start in April 2019 and end in December 2021. The follow up-period will end in Spring 2022, allowing for analysis of data and first assessment of results in Summer 2022. |
| Number of sites | 10 |
| Sample size consideration | Based on the original YEARS cohort, we expect a failure rate of 2.6% (95%CI 1.3-5.2) in both study arms and accept a margin of 2% for defining non-inferiority (12). If there is truly no difference between standard management by CTPA and the YEARS algorithm, then 1566 patients are required to be 80% sure that the upper limit of a one-sided 95% CI (or equivalently a 90% two-sided CI) will exclude a difference in favour of the CTPA group of more than 2%. Using a hierarchical approach, this number approach will be sufficient to have an 80% chance of detecting with a 2-sided alpha level for a superiority of unnecessary CTPAs of 10% between both management strategies if the real difference is above 13% (n=783). |
| Statistical analysis | A non-inferiority analysis will be performed to compare the 3-month symptomatic VTE incidence after a negative CTPA in both study arms. If the upper bound of the confidence interval is above the predefined threshold of 2% (expressed as an absolute risk difference with 1-side 5% alpha level), the non-inferiority hypothesis of the intervention group will be rejected.  A superiority analysis of unnecessary CTPA’s will be carried out if the analysis of the safety outcome is positive (non-inferiority), on all the randomized patients with 2-side superiority test. The Pearson chi-squared will be used with an alpha of 5%.  Exact 95% confidence intervals (CIs) will be calculated around descriptive parameters and observed incidences. |

# Study schedule



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# List of abbreviations

|  |  |
| --- | --- |
| PE | Pulmonary Embolism |
| CDR | Clinical Decision Rule |
| CTPA | Computed Tomography Pulmonary Angiography (CTPA) |
| CT | Computed Tomography |
| VTE | Venous Thromboembolism |
| DVT | Deep Vein Thrombosis |
| CCMO | Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mens gebonden Onderzoek |
| GCP | Good Clinical Practice |
| METC | Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC) |
| (S)AE | (Serious) Adverse Event |
| Sponsor | The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party. |
| Wbp | Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens) |
| WMO | Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen |

# 1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent complication of malignancy(1). Patients with malignancy were associated with a 4-fold risk of VTE compared patients without malignancy, where chemotherapy increased this risk to 6.5-fold(2). The development of VTE is presumed to be due to the production of pro-coagulant molecules by malignant cells and to the pro-coagulant effect of these cells spread into the circulation(3). Furthermore, many factors contribute to the thrombotic risk in malignancy patients, including classical thrombotic risk factors (i.e. age, bed-rest, history of VTE, and comorbid conditions) and risk factors typical of malignancy (i.e. type and stage of malignancy, anti-malignancy treatments)(2, 4, 5).

*Diagnosing PE in patients with malignancy*

Because of its diagnostic accuracy and wide availability, multi-row detector computed tomography pulmonary angiography (CTPA) is currently the imaging test of choice to conﬁrm or exclude acute PE (6, 7). However, this diagnostic test can yield useless or misleading test results if done without appropriate clinical indication (8). Therefore, circulating D-dimer concentrations and clinical predictions rules were developed as complementary diagnostics steps.

The D-dimer is a biomarker that is routinely used in conjunction with clinical parameters in the initial assessment of suspected acute PE(9). Although it is well documented that the D-dimer test is useful in the diagnostic workup of patients with suspected PE, it is thought that the D-dimer test is of less value in patients with malignancy due to often elevated levels in absence of thrombosis (10, 11). According to previous studies, the incidence of normal D-dimer levels (cut off at 0.5μg/mL or age-adjusted) in patients with a malignancy and suspected PE may be as low as 10-15% (12, 13).

Several clinical decision rules (CDRs) have been developed for estimating the pre-test probability of PE. CDR can be combined with D-dimer testing to rule out PE in case of a non-high probability and a normal D-dimer test (14). However, it is recognized that CDRs may not be as effective and safe in patients with malignancy. Recently, the YEARS study combined three elements of the Wells rule (i.e. clinical signs of deep vein thrombosis, hemoptysis, and whether pulmonary embolism is the most likely diagnosis) with D-dimer testing for exclusion of PE, of which the cut-off level is dependent whether YEARS items are absent or not. The study showed that CTPA could safely be avoided in an additional absolute 13% of patients compared with standard algorithms (12). This reduction could be achieved, according to the worst case scenario, at an only 0.78% (95% CI 0.49-1.2) failure rate with regard to the 3-month incidence of recurrent venous thromboembolism. However, this algorithm showed highest failure rates (2.6%, 95%CI 1.3-5.2) in a relatively small subgroup of patients with malignancy (9.7% of the YEARS study population). Moreover, a recent meta-analysis demonstrated that the D-dimer test (cut off <0.5μg/mL), combined with the diagnostic Wells rule, resulted in a similar 2.6% (95% confidence interval (CI) 0.57-11) 3-month failure rate of diagnosing PE in patients with malignancy(13). This was also highest among all subgroups.

As a consequence of unknown safety and efficacy of CDRs in patients with malignancy and presumed futility of D-dimer as a diagnostic test, clinicians-oncologists may often directly order a CTPA when suspecting PE. However, avoidance of CTPA use results in less radiation exposure, contrast material allergy and contrast material induced nephropathy, as well as leads to a reduction of irrelevant sub-segmental emboli detection and health care costs (15-17).

# 2. Study rationale and hypothesis

No (randomized) study has ever compared the safety and efficiency and safety of a diagnostic PE algorithm in patients with active malignancy. A diagnostic algorithm that could safely rule out PE in patients with malignancy without performing CTPAs could improve patient care.

We hypothesize that the YEARS algorithm is non-inferior to management by CTPA with regard to 3-month recurrent VTE rates and will reduce the rate of unnecessary CTPA in patients with clinically suspected PE and active malignancy.

# 3. Objectives

## 3.1 Primary objective

To prospectively validate the safety and efficiency of management according to the YEARS algorithm to safely rule out clinically suspected PE in patients with active malignancy to be compared with ‘standard’ management by CTPA in a randomized study. Safety is defined as the number of recurrent venous thromboembolism during three months follow-up in patients with normal initial diagnostic tests. Efficacy is defined as the number of CT scans performed at baseline.

3.2 Secondary objectives

1. To evaluate the occurrence (timing, location and severity) of recurrent symptomatic VTE during follow-up in both study arms in order to better differentiate between missed PE diagnoses and new onset VTE
2. To compare differences in the rate of isolated sub-segmental PE, defined as CTPA demonstrating an intraluminal filling defect in a sub-segmental artery with no filling defect visualized at more proximal artery levels, in both study arms
3. To assess the occurrence of incidental VTE, defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism(18), during follow up in both study arms
4. To evaluate usage and safety of antithrombotic treatment in both study groups
5. To evaluate practice patterns of anticoagulation therapy during end-of-life care in terminally ill patients with cancer.

# 4. Subjects

## 4.1 Population base

Consecutive patients with clinically suspected PE and active malignancy, who fulfil all the inclusion criteria and meet none of the exclusion criteria, are eligible for inclusion. It is planned to enrol 1566 patients in the Hydra study (see paragraph 4.4 for detailed sample size calculation).

## 4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

* Clinically suspected PE as judged by the treating clinician
* Any type of active malignancy (other than basal-cell or squamous-cell carcinoma of the skin), defined as diagnosis within six months before the study inclusion (as confirmed histologically or high suspicion as judged by the clinician), receiving treatment for malignancy at time of inclusion or during 6 months prior to randomisation, including recurrent or local metastatic malignancy
* Age ≥ 18 years
* Signed and dated informed consent, available for start of the trial procedure

## 4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

* Medical or psychological condition that would not permit completion of the study or signing of informed consent, including life expectancy less than 3 months, or unwillingness to sign informed consent
* Treatment with full-dose therapeutically dosed anticoagulation that was initiated 24 hours or more prior to eligibility assessment
* Contraindication to CTPA
  + contrast allergy

Hemodynamic instability at presentation (as a consequence of concurrent acute PE or otherwise), indicated by at least one of the following:

* systolic blood pressure (SBP) < 100 mm Hg, or heart rate >120 beats per minute or SBP drop by > 40 mm Hg, for > 15 min
* need for catecholamines to maintain adequate organ perfusion and a systolic blood pressure of > 100 mmHg
* Need for cardiopulmonary resuscitation
* Inability to follow-up
* Life expectancy less than 3 months

# 5. Ethical considerations

## 5.1 Regulatory statement

The study protocol and consent forms will be submitted to the Research Ethics Committee. Patient recruitment will not commence before formal approval has been granted. The study will be conducted according to the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice and Hong Kong, Somerset West and Edinburgh) and in accordance with the Guidelines for Good Clinical Practice (CPMP/ICH/135/95 - 17th July 1996).

## 5.2 Inclusion and consent

We will comply with relevant local regulations with respect to patient privacy. A local investigator or study coordinator will give the patient an oral and written explanation about the study and encourage any questions. All participants will be told that participation is voluntary and they are free to leave the study at any time. Because the timeframe for patient recruitment and imaging are critical to the success of the study, research personnel will maintain regular communication with staff in clinical areas where eligible patients are likely to be recruited. After they have given written acknowledgement of informed consent to participate, a medical screening will take place. Through patient interview and review of medical records, it will be confirmed that they satisfy all inclusion criteria and do not meet any of the exclusion criteria.

# 6. Methods

## 6.1 Study design

The Hydra-study is an open, randomized controlled, multicenter international trial with a non-inferiority analysis for the main safety outcome (rate of 3-month VTE in patients not treated with anticoagulants); if non-inferiority has been demonstrated at secondary stage a superiority analysis for the efficiency judgment criterion (rate of unnecessary CTPA) will be performed.

Each adult patient with suspected PE and active malignancy will be randomized to management according to the YEARS algorithm or ‘standard’ management by CTPA only. (Appendix A)

All patients have to sign informed consent before participation.

Patients in whom PE has been diagnosed will be treated with therapeutic doses of anticoagulants according to local hospital guidelines.

All patients, both those in whom PE is excluded and with PE, will be followed for a period of 3 months.

All outcomes that occurred during the 3-month follow-up period will be collected and submitted to an adjudication committee, which will independently assess the occurrence of the outcomes blinded to the group allocation.

## 6.2 Justification for study design

## Although the YEARS algorithm has been shown to lead to safe and efficient exclusion of PE in patients, As a consequence of unknown safety and efficacy of CDRs in patients with malignancy and presumed futility of D-dimer as a diagnostic test, clinicians-oncologists may often directly order a CTPA when suspecting PE. However, avoidance of CTPA use results in less radiation exposure, contrast material allergy and contrast material induced nephropathy, as well as leads to a reduction of irrelevant sub-segmental emboli detection and health care costs. Therefore a randomised study comparing the YEARS algorithm with CTPA only is justified in this vulnerable patient population.

## 6.3 Patient Safety

The study procedures are standard diagnostic test for suspected PE. As per usual clinical care, all patients will be instructed on signs and symptoms of DVT and PE and advised to return to the hospital in case of any suspicion of deep vein thrombosis or PE.

# 7. Specific methods

## 7.1 Baseline clinical examination

The investigator or a delegate will complete a Case Report Form (CRF) to document the study data.

During the screening visit, the investigator or delegate will obtain:

* written informed consent
* demographic data (e.g. age, sex, hospital, length, weight)
* relevant medical history (e.g. heart failure, chronic obstructive pulmonary disease)
* information on symptoms of PE
* data on type, site and staging of active malignancy
* date of malignancy diagnosis
* data on type and timing of malignancy treatment (chemotherapy, radiotherapy, surgery)
* physical exams and measure of vital signs (e.g. body weight, blood pressure, heart rate)
* the following local laboratory results:
  + creatinine clearance
  + D-dimer (in the CTPA group after CTPA is performed)
* CTPA performed
  + diagnosis of PE
  + largest pulmonary vessel involved (sub-segmental, segmental or central)
  + alternative diagnosis
* established anticoagulation treatment

Patients are considered to have symptoms consistent with acute PE if they have sudden onset of dyspnoea and thoracic pain, worsening at deep breathing. In addition, the pulse rate may be increased and signs of DVT of the leg or arm including swelling, tenderness, warmth, and/or erythema of the arm of recent onset (within 10 days) may be present. The following clinical information will be collected by interview: age, immobilization > 3 days, major surgery < 4 weeks, family and personal history of VTE, oestrogen use, anticoagulant treatment, type of malignancy and catheter details. During physical examination the following details will be recorded: body height and weight, localized pain, unilateral swelling of the leg or arm, unilateral pitting edema, superficial vein dilatation and warmth of the leg or arm.

## 7.2 Randomisation

Patients will be randomized into management by either YEARS-algorithm or direct CTPA, on a 1:1 basis and stratified by center.

The randomization process will occur directly after signing informed consent, before a D-dimer test is ordered or at least before the result of an ordered D-dimer test has become available.

*YEARS algorithm*

Patients randomized to the YEARS algorithm will be evaluated according to the YEARS algorithm consisting of three items of the original Wells rule (clinical signs of DVT, hemoptysis and ‘PE most likely diagnosis’) and a D-dimer test (12). In patients without any of the three items and a D-dimer level <1.0 μg/mL, and in patients with ≥1 items and a D-dimer level <0.5 μg/mL a PE is excluded without CTPA. In the other patients a standard contrast enhanced CTPA will be performed according to local practice. PE is defined as at least one filling defect in the pulmonary artery tree on CTPA (6, 7).

*CTPA as single test*

Patients randomized to the CTPA management group will undergo a contrast enhanced CTPA to rule out PE according to standard local practice.

## 7.3 D-dimer test

The D-dimer assay selected for the study will be an automated and well-validated high-sensitive quantitative D-dimer assay (such as: Vidas D-dimer Exclusion®, Biomerieux, Marcy-l’Etoile, France, or Tinaquant®, Roche Diagnostica, Mannheim, Germany, STalia® Diagnostica Stago, Asnieres, France, or others).

## 7.4 CTPA

CTPA will be performed in accordance with local practice. Pulmonary arteries will be evaluated up to and including the segmental vessels from the level of the aortic arch to the lowest hemidiaphragm. Patients will be examined during suspended inspiration or shallow breathing, depending on the degree of dyspnea. Each vessel will be scored for the presence or absence of a clot, including subsegmental vessels, when visualized. A clot will be considered to be present if contrast material outlines an intraluminal defect or if a vessel is totally occluded by low-attenuation material on at least two adjacent slices. The acquisition parameters for multidetector CT will be a total volume of 100 to 120 mL of non-ionic contrast material injected with a power injector at 3 to 5 mL/s; imaging 9 to 20 seconds after initiation of the contrast material injection; scans performed at 1 to 1.3 mm per section with a pitch of 1.25 to 1.75, 120 kV, 115 to 260 mAs; and images reconstructed at 0.6- to 0.8-mm intervals. For obese patients, slice thickness will be sometimes increased to 2.5 mm. The technique for performing and interpreting lung scan and pulmonary angiography has been described elsewhere. PE is defined as at least one filling defect in the pulmonary artery tree on CTPA (6, 7).

## 7.5 Follow-up

All enrolled patients will receive a follow-up call 90 days (+/-7 days) after study inclusion. Clinical follow-up has been shown to be a valid approach to ensure that important clinical outcomes (VTE) are not missed[xx].During this follow-up the following events will be recorded: diagnosis of recurrent DVT, PE, death and hospitalization.

## 7.6 Adjudication of suspected events during follow-up

An independent adjudication committee consisting of two thrombosis specialists not involved in the study will evaluate all suspected clinical events during the 90-day follow-up, i.e. UEDVT, PE or death.

Patients who have a clinically suspected pulmonary embolism will receive CT scanning or perfusion ventilation scanning. PE is diagnosed with CT pulmonary angiography if there is an intraluminal defect in a segmental or greater pulmonary artery. For ventilation-perfusion (VQ) scanning a PE is considered to be present when there is a perfusion defect, segmental or larger on the lung perfusion scan, and there is a mismatch with the concomitant ventilation scan. If the VQ scan is inconclusive, CT pulmonary angiography will be performed. Pulmonary embolism found at autopsy will also be considered diagnostic of VTE.

Patients who have a clinically suspected DVT during follow-up will be examined using CUS or contrast venography using standard clinical protocols. The criteria for diagnosis will be CUS revealing an area > 4mm in thickness of non-compressibility of a venous segment of the lower or upper extremity. DVT will be excluded if an area of non-compressibility is <4 mm.

All deaths during follow-up will be adjudicated as to the likelihood that the death was related to PE. The following criteria will be used: Certain: hypotension, hypoxia, cardiac arrest with no other explanation other than PE and autopsy or radiographic confirmation; highly probable: criteria for certain but another disease could have caused the death; Probable: other cause suspected based on clinical evidence but 100% certainty not available; Unlikely: all other cases.

## 7.7 Treatment

At the moment PE is diagnosed at baseline or follow-up, treatment with therapeutically dosed anticoagulants will be initiated without delay, according to current guidelines [xx] .

## 7.8 Study management

The study will be coordinated from the Leiden University Medical Center in the Netherlands. As described above, the Adjudication Committee will serve to confirm or refute suspected PE and DVT events in the follow-up period.

# 

# 8 SAFETY REPORTING

## 8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 8.2 Adverse events (AEs) and serious adverse events (SAEs)

*Adverse events (AEs)*

Adverse events are defined as any suspected recurrent venous thromboembolism occurring to a subject during the study. All adverse events reported spontaneously by the subject or observed by the investiga­tor or his staff will be recorded.

*Serious adverse events (SAEs)*

A serious adverse event is an objectively proven (fatal) PE or death. The investigator will report all (fatal) PEs and deaths to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the (fatal) PEs and deaths through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for the (fatal) PE and deaths followed by a period of maximum of 8 days to complete the initial preliminary report.

*Follow-up of adverse events*

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study as defined in the protocol.

# 9. Data analyses

## 9.1 Data handling and record keeping

*9.1.1. Data collection and handling*

Data will be collected, used and stored, which concerns data such as name, address, date of birth and medical information. Diligent efforts will be made to ensure the study data are stored securely and confidential information is protected. The handling of personal data will comply with the General Data Protection Regulation (GDPR).

All study participants will receive a study number which is a unique identifier (not based on patient initials and birth date). The key to the code will be safely stored in the local research institute and safeguarded by the principal investigator. The unique study number will be used on the CRF and with the MR images stored in the radiology database. The data that will be sent to the sponsor will only contain the code and not names or other data that can identify study participants. All electronic data and records will be saved under their unique study number and stored in a secured file (in the ‘I drive’) on the computer. Access to study files and electronic records will be restricted to authorized study personnel. The local investigators are responsible for ensuring that all sections of the CRF are completed correctly, and that entries can be verified against source data.

*9.1.2. Storage and Archiving of Data*

The principle investigators will archive all study data (subject identification code list, source data, and investigator's files) and relevant correspondence in the Investigator Site File and this is archived in a closed storage cabinet. Only the principle investigator has access to the subject identification code list and source data. The METC, monitor and the Healthcare and Youth Inspectorate also have access to the data in case of safety reviewing. The Investigator Site File, all source data, and other pertinent documents will be archived for 15 years at the research location.

*9.1.3. Withdrawing consent*

Study participants can withdraw their consent to the use of the personal data at any time. The study data collected until the moment of the withdrawal can be used in the study.

*8.1.4. Processing data*

The Data Protection Officer of the LUMC is responsible for the processing of personal data of the study participants. For questions about rights concerning processing data study participants can contact the Data Protection Officer of the LUMC or the Dutch Data Protection Authority.

## 9.2 Sample size calculation

Based on the original YEARS cohort, we expect a failure rate of 2.6% (95%CI 1.3-5.2) in both study arms and accept a margin of 2% for defining non-inferiority (12). If there is truly no difference between standard management by CTPA and the YEARS algorithm, then 1566 patients are required to be 80% sure that the upper limit of a one-sided 95% CI (or equivalently a 90% two-sided CI) will exclude a difference in favor of the CTPA group of more than 2%. Using a hierarchical approach, this number approach will be sufficient to have an 80% chance of detecting with a 2-sided alpha level for a superiority of unnecessary CTPAs of 10% between both management strategies if the real difference is above 13% (n=783).

## 9.3 Feasibility

To come up with realistic estimates for the feasibility of identifying the required number of study patients, we assessed the number of patients who presented with suspected PE in the presence of malignancy at the LUMC. 175 had a suspected PE during one year. Of these, 25 met one or more of the exclusion criteria, leaving 150 eligible patients in one year. Since it cannot be expected that all eligible patients will consent to study participation, we conservatively estimate that 100 patients can be included in one year. It is expected that 50-100 patients can be included in the other 9 participating hospitals. From this, we are confident that we can complete the study within a 2-year period.

## 9.4 Data analysis

*Primary analysis*

For the primary outcome we will use a per-protocol approach. For the secondary outcome we will use an intention-to-diagnose approach. The difference between approaches is how to report the number of CTPA that are performed but not indicated by the strategy. By using this approach, PE diagnosed at presentation on a CTPA that is not indicated is considered to be a failure of the diagnostic strategy.

A non-inferiority analysis will be performed to compare the 3-month symptomatic VTE incidence after a negative CTPA in both study arms. If the upper bound of the confidence interval is above the predefined threshold of 2% (expressed as an absolute risk difference with 1-side 5% alpha level), the non-inferiority hypothesis of the intervention group will be rejected.

A superiority analysis of unnecessary CTPA’s will be carried out if the analysis of the safety outcome is positive (non-inferiority), on all randomized patients with 2-side superiority test. The Pearson chi-squared will be used with an alpha of 5%.

Exact 95% confidence intervals (CIs) will be calculated around descriptive parameters and observed incidences.

*Secondary analyses*

All secondary outcomes will be compared using appropriate usual test according to the distribution of variables.

The secondary combined endpoint of 3-month symptomatic and incidental VTE will be compared according to the primary endpoint analysis.

# 10. Potential Challenges

We anticipate some potential challenges in the implementation of this protocol. Because patients with suspected PE in the presence of malignancy will be recruited from the inpatient wards, Emergency Department and Thrombosis Clinic, the physicians and nurses recruiting for the study will have to remain vigilant to ensure that potential participants are not missed. Intensive education of staff about the study through in-services and posters reminding them to refer patients with suspected PE will be used. Within every participating hospital we will form a multidisciplinary group consisting of the study oncologist, diagnostic radiologist and trial nurse. They are asked to guarantee the randomised study design throughout the study.

# 11. Ethical and legal aspects

## 11.1 Ethical Considerations

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by good clinical practice and the ethical principles described in the Declaration of Helsinki (2013 version). The study will be carried out in keeping with local legal and regulatory requirements.

## 11.2 Subject Information and Informed Consent

Before being admitted to the study, the subject must consent to participate after being fully informed about the nature, scope, and possible consequences of participation. The consent documents must be in a language understandable to the subject and must specify who informed the subject. After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed informed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. If the subject has a primary physician, the investigator should inform the subject’s primary physician about the subject’s participation in the study - provided the subject agrees to the primary physician being informed.

## 11.3 Confidentiality

The name of the subjects and other confidential information are subject to medical professional secrecy. For the primary and secondary analysis, only anonymized information that is included in the standardized paper CRF forms can be used. This information is depersonalized and stored under an individual identification code that is assigned to each patient at inclusion after signing informed consent. The study patients will declare in the written consent to release the investigator from the medical professional secrecy to allow identification of subject’s name and/or inspection of original data for monitoring purposes by health authorities and authorized persons (monitors).

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. Study findings stored on a computer will be kept safe in accordance with local data protection laws and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of data legislation will be fulfilled in its entirety.

## 11.4 Responsibilities of principal investigators

The principal investigators will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions.

The principal investigators will maintain a list of sub-investigators and other appropriately qualified persons to whom they have delegated significant study-related duties.

## 11.5 Approval of Study Protocol

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee/institutional review board of the LUMC in Leiden. The document of final approval by the independent ethics committee should mention the title of the study, the study code, all study sites, the documents they reviewed, and the date of decision. Before the first subject is enrolled in the study, all ethical and legal requirements must be met. The investigator must keep a record of all communications with the independent ethics committee and the competent authorities.

## 11.6 Ongoing information for independent ethics committee

*11.6.1 Amendments*

The competent authorities including the independent ethics committee must be informed of all subsequent protocol amendments and administrative changes, in accordance with the respective local legal requirements. Amendments must be evaluated to determine whether formal approval should be sought and whether the informed consent document should also be revised. The independent ethics committee must be informed of all subsequent protocol amendments which require formal approval in accordance with the legal requirements.

*11.6.2 Annual progress report*

The coordinating investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/ serious adverse reactions, other problems, and amendments.

*11.6.3 End of study report*

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last follow-up visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

*11.6.4 Public disclosure and publication policy*

The results of this study will be disclosed unreservedly according to the Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy (<http://www.ccmo.nl/attachments/files/ccmo-statement-publicatiebeleid-3-02-en.pdf>).

## 11.7 Anticipated Results and Conclusions

We expect that this study will show that the YEARS diagnostic algorithm applied in cancer patients with suspected PE will lead to a safe exclusion of the disease in question and will lead to avoidance of performing unnecessary CTPA’s leading to less radiation exposure, contrast material allergy and contrast material induced nephropathy, as well as leads to a reduction of irrelevant sub-segmental emboli detection and health care costs.

## 11.8 Insurance

The sponsor has a liability insurance which is in accordance with article 7of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the

Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical

Research in Humans of 2015). This insurance provides cover for damage to research

subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

# 12 Agreements

## 12.1 Financing of the study

This study will be financed by unrestricted grants from the participating hospitals.

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## 12.2 Publication

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentation, etc.) by the investigators or their representatives, shall require the approval of the principal investigators. It is planned to publish the results of the study as an original article in an appropriate medical journal as well as to present the results at international congresses. The choice of the journal for the publication will be made by the principal investigators in agreement with the co-authors. Besides the principal investigators, further authors of this article must meet the following criteria:

* Substantial contribution to the recruitment of subjects, i.e. inclusion of at least 5 study subjects;
* Substantial contribution to the interpretation of the data;
* Substantial contribution to drafting the article or revising it for intellectual content

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# Appendix A: Flowchart