

**PERC rule to exclude the diagnosis of pulmonary embolism in emergency low risk patients :
a non inferiority randomized controlled trial.**

The PROPER study

BIOMEDICAL RESEARCH PROTOCOL

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The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

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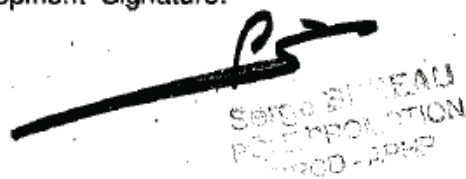
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1 SUMMARY

Full title	The Pulmonary Embolism Rule Out Criteria (PERC) rule to exclude the diagnosis of Pulmonary Embolism in emergency low risk patients: a non inferiority randomized controlled trial
Acronym	PROPER
Coordinating Investigator	Yonathan Freund, emergency department, Hopital Pitié-Salpêtrière, Paris
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	The diagnosis of Pulmonary Embolism (PE) in the Emergency Department (ED) is crucial. As emergency physicians fear to miss this potential lethal condition, PE tends to be overdiagnosed with potential source of unnecessary risks and no clear benefit in terms of outcome. PERC is an 8-item block of clinical criteria that can identify patients who can safely be discharged without further investigation in the ED for the diagnosis of PE. The endorsement of this rule could markedly reduce the number of irradiative imaging studies, length of stay in the ED, and rate of adverse event resulting from both diagnostic and therapeutic means. Several retrospective and prospective studies have shown the safety and benefits of PERC rule for PE diagnosis in low risk patients. However, no randomized study has yet compared the benefit/risk ratio of PERC based strategy with the standard diagnosis strategy and thus validated its endorsement in this setting. We hypothesize that in patients with a low gestalt clinical probability and a PERC negative, PE can be safely ruled out and the patient discharged with no further testing
Primary objective and assessment criterion	The primary objective of this study is to assess the non inferiority of a PERC based diagnosis strategy for PE low

	<p>risk emergency patients, compared to the standard strategy of D-dimer testing, on the occurrence of non-diagnosed thrombo-embolic event.</p> <p>The primary outcome is the failure percentage of the diagnostic strategy, defined as diagnosed DVT or PE at 3 month follow up, among patients for whom PE has been initially ruled out. Exclusion of PE in the ED is made upon negative D-dimere result or negative CTPA in both groups, or negative PERC in the intervention group.</p>
Secondary objectives and assessment criteria	<p>To assess the reduction of unnecessary irradiative imaging studies and adverse events. To assess the reduction in ED length of stay, undue onset of anticoagulation regimen and associated adverse events. To assess the reduction of hospital admission, readmission, and mortality at 3 months.</p> <p>Secondary endpoints include:</p> <ul style="list-style-type: none"> - Rate of CTPA and related adverse events - Length of stay in the ED (hours) - Anticoagulant therapy administration and adverse events - Admission to the hospital following ED visit. - All causes re hospitalization at 3 months, - Death from all causes at 3 months
Experimental design	<p>This is a controlled, cluster randomized trial.</p> <p>Each center will be randomized on the sequence of period intervention: 6 months intervention (PERC based strategy) followed by 6 months control (usual care), or 6 months control followed by 6 months intervention with 2 months of "wash-out" between the two periods.</p>
Population involved	Adult emergency patients with a low clinical suspicion of PE
Inclusion criteria	<p>Acute onset of, or worsening of dyspnea Or chest pain</p> <p>And a low clinical pretest probability of PE, empirically estimated by the gestalt.</p>

	And a signed informed consent
Non-inclusion criteria	<p>Other obvious cause than PE for dyspnea or chest pain</p> <p>Acute severe presentation</p> <p>Contra-indication to CTPA</p> <p>Concurrent anticoagulation treatment</p> <p>Current diagnosed thrombo-embolic event</p> <p>Inability to follow up</p> <p>Prisoners</p> <p>Pregnancy</p> <p>No social security</p> <p>Participation in another intervention trial</p>
Practical procedures	Each center will recruit patients for two 6-month periods, one experimental and one control, the order of the period being randomized.
Procedures added by the research	<p>In the control group, emergency physician will assess low risk patients for PE with the conventional strategy, using D-dimer testing with subsequent CTPA if positive.</p> <p>In the experimental group, emergency physician will assess low risk patients for PE first with calculation of PERC score. If all PERC criteria are negative, then no further testing for PE is recommended. If at least one criterion is positive, then the patient undergoes D-dimer testing, with subsequent CTPA if positive.</p>
Risks added by the research	<p>The added risk for a patient recruited in the experimental group is the one of a false negative PERC score, whilst the patient has actually a PE. This risk has been reported to be below 2% in previously cited meta-analysis, while the risk of conventional strategy is roughly of 1%.</p> <p>This threshold of 2% has been reported to be the one below which the risks are outbalanced by benefits, namely reduction of CTPA and related adverse events and undue anticoagulation regimen therapy. Furthermore, potentially missed PEs would be of very low risk – an overall risk below 2/10 000.</p>
Number of subjects	1920

chosen	
Number of centres	15
Research period	Total duration of the study : 17 months and 6 months to carry out the last follow-up Duration of participation of each patient : 3 months Duration of recruitment: 14 months (2 periods of 6 months with a 2 months wash out period).
Number of inclusions expected per centre and per month	10.6
Statistical analysis	No interim analysis is planned. Non inferiority evaluation of the PERC strategy will be assessed on per protocol population using the confidence interval approach.
Funding source	APHP
Data Safety Monitoring Board anticipated	No

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 Hypothesis for the research

The Pulmonary Embolism Rule Out Criteria (PERC) is an 8-item rules of clinical criteria ¹. PERC negative patients are those with a PERC score of zero, defined by the eight following criteria:

- Age less than 50 years
- Heart rate less than 100 beats per minute
- No prior history of thrombo-embolic event
- Oxygen saturation greater than 94%
- No trauma or surgery in the past four weeks
- No hemoptysis
- No exogenous estrogen intake
- No unilateral leg swelling

We hypothesize that in patients with a low gestalt clinical probability (Appendix 1) and a PERC negative, pulmonary embolism (PE) can be safely ruled out and the patient discharged with no further testing

2.2 Description of knowledge relating to the pathology in question

The incidence of pulmonary embolism (PE) in France and Europe has been estimated to 0.6-0.9 per 1000 persons per year ^{2,3}. PE is a potential lethal diagnosis ⁴, and its diagnosis in the Emergency Department (ED) is challenging ⁵.

The fear of missing this diagnosis and the poor specificity of its clinical presentation lead physicians to suspect PE in all patients who present with a broad variety of symptoms such as dyspnea, chest pain, syncope, and hypotension. This represents a volume of ED patients of more than 10 million a year in the United States. For the last decade, the standard strategy for PE diagnosis is as presented in figure 1.

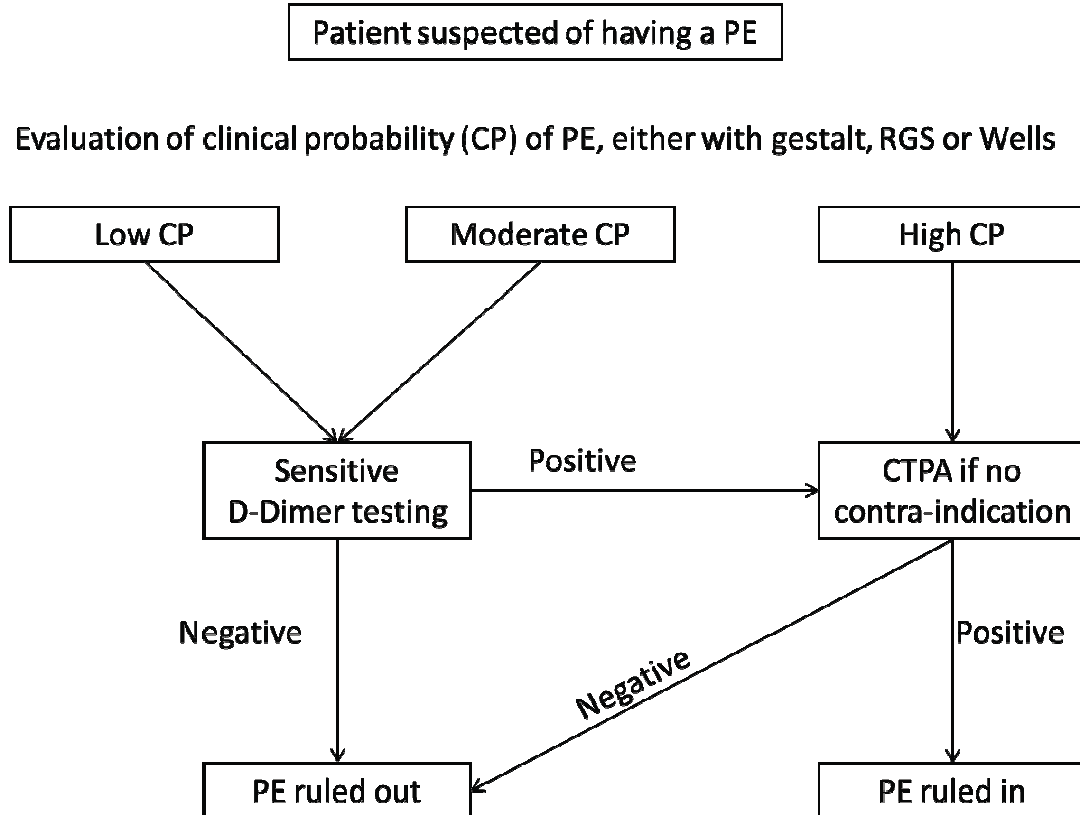


Figure 1: Standard strategy: recommended diagnosis work up for PE in the emergency department. PE: Pulmonary Embolism, RGS: Revised Geneva Score, CTPA: Computed Tomography of Pulmonary Artery.

The usual work up for PE diagnosis first includes an assessment of clinical probability of having a PE. This assessment can be made using a structured score (Revised Geneva Score RGS or Wells score^{6,7}), or an unstructured estimation of the clinical probability (referred to as the clinician “gestalt”⁸⁻¹⁰) (cf Appendix 1). Then a sensitive D-dimer testing in patient with low to moderate clinical probability, followed if positive by a Computed Tomography Pulmonary Angiogram (CTPA) in the absence of contra-indication while patients with a high clinical probability should undergo CTPA without the need for preliminary testing. This diagnosis strategy is recommended by European guidelines¹¹, national expert recommendations¹² and local policies. It has been validated and is safe to exclude PE in outpatient visiting ED¹³. However, due to its low specificity (40-60%^{10,14}), D-dimer testing may lead to more than 50% of false positive and subsequent CTPA¹⁰. Furthermore, the wide availability of D-dimer testing combined to the fear of missing a PE led to a lowering in the threshold for testing patients for PE, hence the decrease in the

prevalence of confirmed PE amongst suspected patients from 30% to below 10% in the US^{1,15-17}.

Subsequently, there was in the last 15 years a marked rise (up to 15 fold) in the utilization of CTPA¹⁸ and in the incidence of diagnosed pulmonary embolism¹⁹. However, this greater incidence of PE was not followed by a decrease in mortality from PE, but rather a decrease in PE fatality^{19,20}. This suggests that PE tends to be “overdiagnosed”: small PEs are more frequently diagnosed, with no clear benefit in terms of outcomes. This increased exposure to CTPA may be a source of unnecessary risks, such as contrast-induced nephropathy and allergic reactions, adverse events after anticoagulation treatment or the delayed occurrence of radiation-induced cancer²¹⁻²³.

2.3 Summary of relevant pre-clinical experiments and clinical trials

Assessing the risk benefit ratio for PE investigation, it has been calculated (using Pausker and Kassirer method²⁴) that if the pre test probability is below 1.8%, patients should not undergo D-dimer testing because a positive result would mandate a CTPA, which would have a negative benefit risk ratio¹.

To reduce the rate of unnecessary testing for PE caused by overuse of D-dimer, Kline et al. developed in 2004 a block rule of eight binary variables (PERC rule): age <50 years, pulse <100bpm, SaO₂ >94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no prior PE or deep venous thrombosis and no exogene estrogen use¹ – PERC negative patients are defined as fulfilling these 8 criteria. Kline et al. applied this rule in their princeps study to low clinical probability patients, defined by a gestalt empirical clinical probability less than 15%^{1,16}. They reported that the prevalence of PE for PERC negative patients was 1.4% (95% CI 0.5% to 3%). This low rate suggests that PERC negative patients could be safely discharged after clinical examination without further testing. Moreover, the rate of 1.4% is below the reported upper limit of false negative rate after pulmonary angiogram or CTPA (3%)^{13,25,26}, which advocates for a safe alternative to further testing.

Following this princeps study, several other studies assessed the safety of a PERC based policy to exclude PE in low risk emergency patients with a PERC negative score. Two meta-analyses^{17,27} confirmed the benefits and safety of PERC rule, with a rate of PE after follow up lower than 1% in PERC negative patients. They comprised only non interventional studies, 10 prospective and 3 retrospective studies, accounting for a total

of 14 844 ED patients with a suspicion of PE. Amongst these 13 studies included in the meta-analyses, 3 were conducted in Europe (France, Belgium and Switzerland)²⁸⁻³⁰.

In the first two European studies^{28,29} the prevalence of PE amongst PERC negative patients was 5.4% and 6.7% (95%CI 3% to 10%). Their authors argued that the higher prevalence of PE in Europe (>20%¹⁷) than in the US (<10%¹⁷) is the main reason for this lower negative predictive value, and that this rule should not be applied in high prevalence population. These first disappointing results had led to the reluctance of European physicians to rely on the PERC rule for excluding PE in low risk patients. However, these two studies had several methodological biases: both studies were retrospective, and did not collect PERC items prospectively. Moreover the studied samples were not solely patients with a low gestalt clinical probability: they included unselected patients with suspected PE in the ED, with low to high pre test clinical probability. Although authors from one study ran a sensitivity analysis focusing on patients with low PTP, this was assessed using Revised Geneva Score that can be seen as redundant with PERC items. These specific limits, coupled with the greater prevalence in the European studies might explain the greater rate of false negative.

A few years later, in 2012, Penalzoza et al. reported that PERC rule is safe even in Europe, when combined with a low gestalt clinical probability³⁰ with the absence of thrombo-embolic event after 3-month follow up among the included patients. Accordingly, in a recent multicenter retrospective study, we also observed a very low prevalence of PE (0.5% [95% CI 0.1 – 1.1%]) amongst low risk, PERC negative emergency patient³¹.

Of note, all of the previously cited studies were either prospective or retrospective, but no randomized study has yet compared the benefit/risk ratio of PERC based strategy versus the standard diagnosis strategy (Fig. 2), on occurrence of undiagnosed PE in low risk patients.

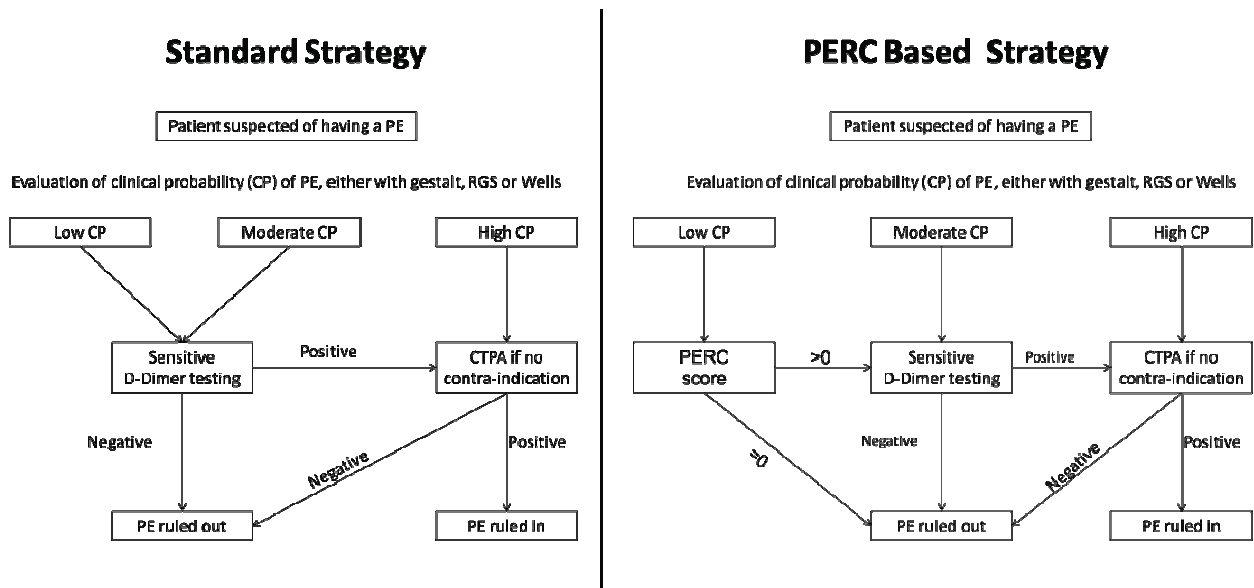


Figure 2: Standard strategy and PERC based strategy for the diagnosis work up of PE in the Emergency Department.

2.4 Description of the population to be studied and justification for the choice of participants

As it has been detailed in previous major diagnostic studies on PE ^{32,33} this study will include patients with a suspicion of PE defined as acute onset of new or worsening shortness of breath or chest pain, in the absence of any obvious other cause (such as pneumothorax, asthma attack, ST elevation myocardial infarction, trauma, etc.) associated with a low empirical clinical probability estimated by the clinician gestalt.

As described in previous studies ^{1,30}, this assessment is established as the answer of the question “How do you estimate the pre-test clinical probability: low, moderate, or high? ¹⁰”

2.5 Summary of the known and foreseeable benefits and risks for the research participants

Pulmonary Embolism is a diagnosis that concerns nearly 200 000 patients each year in France. The multiplication of diagnostic studies led to a rise in PE diagnosis, associated with a concurrent rise in the diagnosis of less severe PE, and no subsequent decrease in mortality ^{18–20}.

According to many retrospective studies including ours, the rate of PERC negative patients amongst patients with a low clinical probability of PE range from 15% to 30% ^{1,28,30,31}. If

PERC have been used in place of a conventional D-dimer based diagnostic strategy, more than 10% of CTPA could have been avoided ^{31,34}.

Such reduction in imaging studies would be beneficial for patients. Newman and Schriger extrapolated that the potential harm resulting from the three major risks of further testing outweighs the benefit in PERC negative patients ³⁵. The main medical harms that can be caused by unnecessary testing for PE include adverse events from CTPA, delayed solid tumor increased risk from irradiative imaging, and iatrogenic complication of anticoagulation for positive tested patients (either false or true positive). Moreover, the benefits of diagnosing PE in low risk patients are unclear. Mortality for patients with suspicion of PE seems very low: Kline reported that among more than 8000 patients tested for PE in the ED, only 13 patients (0.2%) died because of PE ³⁶.

In 2011, Newman and Schriger extrapolated the risks and benefit of D-dimer testing among a sample of 10,000 PERC negative patients ³⁵. This supplemental testing could lead to the diagnosis of 30 PE that would have been missed (credible interval 6-60). However, further testing in these 10,000 PERC negative patients may cause 73 adverse events (14 – 140) among which 36 fatal events (4 – 69). The causes of adverse events were acute renal failure from contrast induced nephropathy (50 per 10,000 patients), severe hemorrhage due to anticoagulation treatment (17 per 10,000 patients), and cancer resulting from radiation (5 per 10,000 patients)

Besides the estimated unfavorable medical benefit/risk ratio for the patient, further testing has clear downsides: a prolonged stay in the ED, with potential subsequent overcrowding ^{37,38}, overall worse short term outcomes ³⁹, and increased cost.

In a retrospective study, median CTPA time in the ED has been reported to be 160 min, accounting for more than half of total ED length of stay ³⁴. ED times could be greatly reduced if PERC was endorsed: nearly a quarter of patients with a low pretest probability could be discharged upon physical examination, without the need for time consuming biological and imaging studies and subsequent overcrowding.

Finally, avoiding any supplemental investigations for PERC negative patients may also reduce the cost of ED visits, which would be of great benefit in the context of increasingly resource stretched healthcare services. Thus, in case of the demonstration of non-inferiority, the PERC based strategy compared to the standard strategy will safely and substantially reduce the volume of D-dimer and CTPA testing, and therefore irradiation, adverse events, length of ED stay and overcrowding.

The risk for a patient recruited in the experimental group is the one of a false negative PERC score, whilst the patient has actually a PE. This risk has been reported to be below 1% in previously cited meta-analysis. Furthermore, potential false negative patients would belong to the group of PE of lower risk, with an estimated 30 days mortality below 1%⁴⁰⁻⁴² – on top of the overall mortality rate estimated in the conventional group (0.2%³⁶), the overall extrapolated added risk would be below 1/10 000 at 30 days in the experimental group.

3 OBJECTIVES

3.1 Primary objective

The primary objective of this study is to assess the non inferiority of a PERC based diagnosis strategy for PE low risk emergency patients, compared to the standard strategy of D-dimer testing, on the occurrence of non-diagnosed thrombo-embolic event.

3.2 Secondary objectives

The secondary objectives are the following:

- 1) to assess the reduction of unnecessary irradiative imaging studies and adverse events
- 2) to assess the reduction in ED length of stay, undue onset of anticoagulation regimen and associated adverse events
- 3) to assess the reduction of hospital admission following the ED visit, hospital readmission, and mortality at 3 months.

4 PLAN FOR THE RESEARCH

4.1 Concise description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

The primary outcome is the failure percentage of the diagnostic strategy, defined as diagnosed deep venous thrombosis (DVT) or PE at 3 month follow up, among patients for whom PE has been initially ruled out.

Exclusion of PE in the ED is made upon negative D-dimere result or negative CTPA in both groups, or negative PERC in the intervention group.

Follow up at 3 months will be made upon telephone interview of the patient or his general practitioner, outpatient consultation or hospital visit. The primary criterion of thrombo-

embolic event will be based on an objective diagnosis of DVT on Doppler ultrasonography, an intraluminal defect on CTPA, or a V/Q lung scan with a reported high probability. To confirm the occurrence of the primary endpoint, all files with evidence of thrombo-embolic event collected by the local investigator of each center will be independently reviewed by an adjudication committee of three experts, blinded one to each others, and blinded to the study group. The adjudication committee will also review cases of death with no evidence of thrombo-embolic event and will adjudicate the death as likely related to a PE or not. A sudden death in the absence of other obvious cause will be adjudicated as related to a PE.

4.1.2 Secondary assessment criteria

Secondary endpoints will include:

Rate of CTPA in the ED at day 0

Rate of CTPA related adverse events, defined as anaphylactoid reaction requiring therapeutic intervention within 24 hours, and contrast induced nephropathy with documented >25% increase in creatinine level within three months

Length of stay in the ED (hours)

Admission to the hospital following the ED visit

Anticoagulation therapy administration (number of day with treatment within three months)

Rate of severe hemorrhage in patients with anticoagulation therapy, defined as fatal or life-threatening, requiring blood transfusion, requiring hospitalization, or that originates a decrease of more than 2 g/dl of haemoglobin in seven days ⁴³

All causes re hospitalization at three months

All causes death at three months

4.2 Description of research methodology

4.2.1 Experimental plan

This is a prospective multicenter, cluster randomized, non inferiority controlled study. Each center will be randomized on the period: six months intervention followed by six months control, or six months control followed by six months intervention. The design, conduction and reporting of this study will follow the CONSORT statement extended to cluster randomized trial ⁴⁴.

Justification for cluster randomization

In this study, cluster randomization design was preferred to an individual randomization (RCT-randomized controlled trial) to enhance the feasibility of the study by all the centers, in particular regarding the recruitment. Eligible patients are suspected to have a pulmonary embolism (i.e. a potentially life threatening condition). In this emergency setting, we hardly believe that centralized randomization at patient level is likely to make patients inclusion less feasible. We also consider that an individual randomization might expose to a contamination bias because the investigators will be aware (not blinded) of the two different strategies tested in the study. Any contamination bias (e.g. use of PERC score in the control group) is less likely to happen in a cluster randomization design because both strategies are not conducted during the same period in the same center. Furthermore, as expressed by Edwards et al, it is not unethical to endorse a cluster randomization design considering that we have warranted safeguards such as informed consent prior to recruitment⁴⁵.

The two groups will have a different work up for the diagnosis of PE in the ED as follows:

Experimental group:

PERC based strategy: work up for diagnosis of PE includes calculation of PERC. If all PERC criteria are negative, no further testing for PE is recommended. If at least one criterion is positive, then the patient undergoes sensitive D-dimer testing, with subsequent CTPA if positive. In case of negative D-dimer result, PE will be excluded.

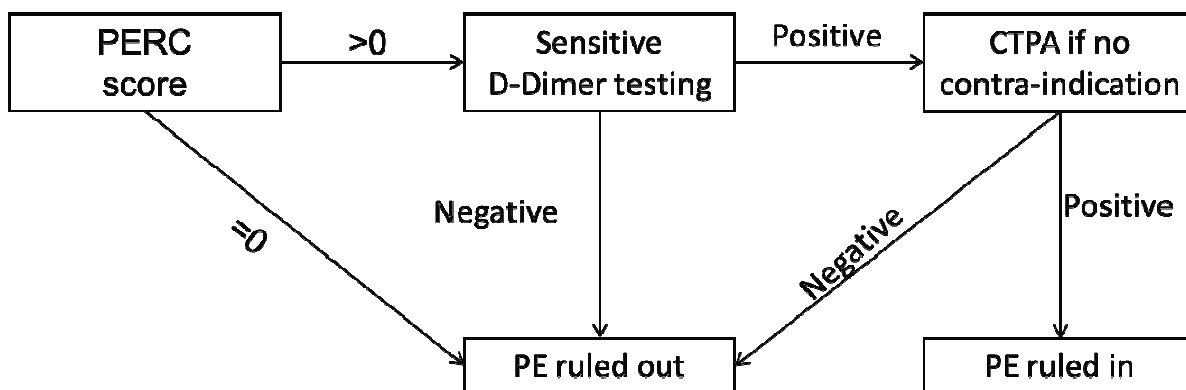


Figure 3a: Experimental group: PERC based strategy for patients with low clinical probability.

Control group:

Standard strategy: conventional work up for diagnosis of PE. Every low risk patient will undergo sensitive D-dimer testing, with subsequent CTPA if positive. In case of negative D-dimer, PE will be excluded.

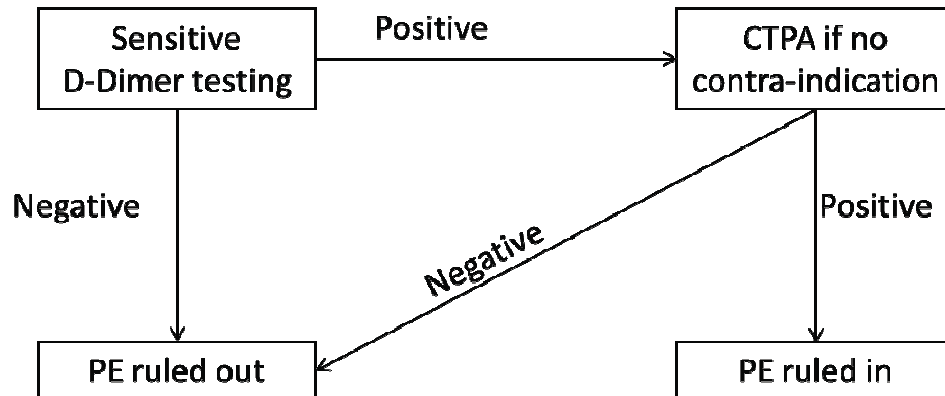


Figure 3b: Control group: Standard strategy for patients with low clinical probability.

4.2.2 Case for Age-adjusted D-dimer

It has been recently reported that the cut off for positive D-dimer should be changed for patients aged >50 years to $\text{Age} \times 10 \text{ ng/ml}$ ⁴⁶. This strategy has been validated in a large multicenter international trial⁴⁷. This strategy is actually endorsed by our centers. The strategy for defining “positive D-dimer” ($\text{age} \times 10 \text{ ng/ml}$ for patients older than 50 years) will be stated before the start of the study in each center and shall not change during the recruitment period. Of note, this change will only affect patients aged 50 or greater, hence no PERC negative patients. Therefore, there will be no interference with our objectives. Negative D-dimer will then correspond to a result $< 500 \text{ ng/ml}$ for patients aged under 50, and to a result $< \text{age} \times 10$ for older patients. A positive result will be a result equal or positive to these threshold.

4.2.3 Number of centres participating

This is a national multicenter study, with patients included from 15 French EDs (cf list in Appendix 2)

4.2.4 Identification of the subjects

For this research, the subjects will be identified as follows:

Centre No. (3 numerical positions) - Selection order No. of the person in the centre (4 numerical positions) - surname initial - first name initial

This reference is unique and will be retained for the entire research period.

4.2.5 Randomisation

Sites period randomization will be prepared by URC-Est using permutation (SAS 9.3) before the first site initiation visit.

4.2.6 Blinding methods and provisions put in place to maintain blindness

Patients will be followed up at 3 months by phone call and/or post mail. All thrombo-embolic events or death that occurred in the 3 month period of follow-up will be collected and submitted to an adjudication committee, which will independently assess the occurrence of the primary outcome blind to the group allocation.

5 PROCEDURE FOR THE RESEARCH

5.1 Inclusion visit

For the study period, patients that attend to one of the participating center will be screened for eligibility by emergency physicians and research assistant. When a patient is screened eligible, his written informed consent will be sought. In case of inability to consent, the patient will not be included in the study.

Subjects whose consent is sought	Who informs the subject and collects their consent	When is the subject informed	When is the subject's consent collected
The patient	Local investigator Or emergency physician in charge	In the ED, before PE Work up	In the ED, before PE Work up

All patients with chest pain or dyspnea will be screened and included in the ED by emergency physicians and research assistant. If the treating emergency physician or local investigator considers that the patient has a sufficient clinical suspicion of PE that he needs formal work up for this diagnosis, and that this suspicion is low enough to discard this suspicion in case of negative D-dimer, then the patient will be eligible and asked for written informed consent.

When recruiting a patient, the emergency physician or local investigator will have to confirm in written that he answered “yes” to the two following sentences:

This patient has a clinical suspicion of Pulmonary Embolism, and this diagnosis needs to be formally ruled out or confirmed before discharge

I estimate the empirical clinical probability of Pulmonary Embolism as low

After written informed consent has been obtained, the patient can be included in the study.

5.2 Follow-up Visits

Included patients will be followed up by phone interview or hospital visit at three months (13 weeks) by a clinical research technician. The time frame of three months could be subject to minor adjustment, and will occur between day 84 and day 98. Follow up visit or interview will seek the occurrence of thrombo-embolic event (DVT documented with ultrasonography of the lower limbs or venous CT, or PE documented with positive CTPA or high probability V/Q lung scan), death, return visit to the ED, hospitalisation.

All medical record pertaining to the patient from this timeframe will be sought and analysed by the local investigator, to found report of thrombo-embolic event, or adverse events from CTPA or anticoagulation. In the cases of death, or report of a thrombo-embolic event, the file will be analysed by a comitee of three independent experts.

This method of adjudication has been described and validated in all major previous diagnostic studies on PE ^{32,33}.

5.3 Expected length of participation and description of the chronology and duration of the research.

Each center will have 2 periods of recruitment of 6 months. A wash-out period of 2 months is planned between the two recruitment periods. Thus total inclusion period will last 16 months.

Patient duration of follow-up will be 3 months. The total duration of the study will be 17 months and 6 months to carry out the last follow-up.

Duration of each period of recruitment in each center could be shorter, as each center will close recruitment once the target is reached, to ensure similar recruitment in the two periods.

Maximum period between selection and inclusion	24 hours
Inclusion period	14 months
The included subjects' length of participation, of which:	
Follow-up period:	3 months
Total research period:	17 months and 6 months to carry out the last follow-up

5.4 Table or diagram summarising the chronology of the research

Actions	Day 0 (Inclusion visit)	Month 3
Informed consent	X	
History	X	
Clinical exam*	X	
Para-clinical exam (D-dimer +/- CTPA if indicated)	X	
PERC score calculation	X	
Adverse events (including thrombo-embolic event)	X	X

5.5 Distinction between care and research

TABLE: Distinction between procedures associated with "care" and procedures added because of the "research"

Procedures and treatments carried out as part of the research	Procedures and treatments associated with <u>care</u>	Procedures added because of <u>the research</u>
Follow up by phone or mail at 3 months		X
PERC Score		X
D-dimer testing	X	
CTPA if D-dimer positive	X	

5.6 Termination rules

5.6.1 Criteria and methods for prematurely terminating the research

5.6.1.1 Criteria and methods for the premature termination of the research

Any subject can withdraw from participating in the research at any time and for any reason.

The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If a patient is lost to follow up, the local investigators and research assistants will try to contact him, his next of kin, or his family practitioner

If a patient is lost to follow up, but there is a record of him meeting the primary criteria, data relating to the subject can be used in the final analysis unless an objection was recorded when the subject signed the consent form.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. Practically, the subject will be excluded from the research.

The case report form must list the various reasons for ending participation in the research:

Ineffective

Adverse reaction

Other medical problem

Subject's personal reasons

Explicit withdrawal of consent

5.6.2 Follow-up of the subjects after the premature termination of research

Ending a subject's participation does not affect the normal management of the subject's illness in any way.

If there are serious adverse events, the investigator must notify the sponsor and monitor the subject for 6 months.

5.6.3 AP-HP as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Adult that presents to an ED
 With new onset of or worsening of shortness of breath or chest pain
 And a low clinical probability of PE, estimated by the clinician gestalt (cf Appendix 1)
 And informed consent signed.

6.2 Non-inclusion criteria

Other obvious cause than PE for dyspnea or chest pain
 Acute severe presentation (clinical signs of respiratory distress, hypotension, SpO2<90%, shock)
 Contra-indication to CTPA (allergy, or creatinine clearance less than 30 mL/min)
 Pregnancy
 Concurrent anticoagulation treatment
 Current diagnosed thrombo-embolic event
 Inability to follow up
 No social security
 Prisoners
 Participation in another intervention trial

6.3 Recruitment methods

	Number of subjects
Total number of subjects needed	1920
Number of centres	15
Inclusion period (months)	12
Number of subjects/centre	135
Number of subjects/centre/month	10.6

In participating centers, patients with suspicion of PE represent a high volume of ED visit.

Previous retrospective studies ^{6,32,33} in these centers confirm that the potential for
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recruitment exceeds 30 eligible patients per month, from whom roughly 40% have a low gestalt clinical probability of PE ³⁰. Moreover, previous prospective studies with similar inclusion criteria achieved comparable recruitment target. Expected number of patients recruited in the participating centres is as follows:

	Name	First Name	Town	Country	Expected recruitment per month	Total
1	Freund	Yonathan	Paris	France	15	180
2	Ray	Patrick	Paris	France	12	144
3	Pateron	Dominique	Paris	France	14	168
4	Choquet	Christophe	Paris	France	10	120
5	Truchot	jennifer	Paris	France	14	168
6	Feral-Pierssens	Anne-Laure	Paris	France	10	120
7	Doumenc	Benoit	Paris	France	8	96
8	Beaune	Sebastien	Boulogne	France	8	96
9	Khellaf	Mehdi	Créteil	France	8	96
10	Charpentier	Sandrine	Toulouse	France	10	120
11	Tazarourte	Karim	Lyon	France	10	120
12	Desmettre	Thibaut	Besançon	France	10	120
13	Wargon	Mathias	Bry s Marne	France	8	96
14	Adnet	Frederic	Bobigny	France	8	96
15	Joly	Luc-Marie	Rouen	France	15	180
Total					160	1920

7 **ASSESSMENT OF EFFICACY**

7.1 **Description of parameters for assessing efficacy**

Diagnosis of thrombo-embolic event will be made using usual criteria ⁴⁷:

For DVT: on the basis of an abnormal result on proximal compression ultrasonography

For PE: on the basis of a CTPA or angiography showing intraluminal defect, or a Ventilation/Perfusion lung scan showing a high-probability pattern.

7.2 **Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing efficacy**

Recruited patients will be followed up at 3 months by phone interview and/or mail, or hospital visit in case they are still hospitalised. The primary endpoint is the occurrence of a thrombo-embolic event that has not been diagnosed in the ED at the inclusion visit (DVT or PE). A structured questionnaire will assess this eventuality of this occurrence. Patients will be asked whether they have had another visit to the hospital or physician appointment, and whether they had diagnostic tests for thrombo-embolic event (namely lower limbs

Doppler ultrasound, CTPA or V/Q scan). They will also be asked whether an anticoagulation treatment was introduced during the follow up period.

All suspected events will be collected, and their complete medical files will be sent for external adjudication of the primary endpoint by an adjudication committee of three independent experts, blinded to each other and blind to the group allocation of the patient. All major cardiovascular events (cardiac arrest, shock, myocardial infarction) or death will be sent to the adjudication committee for expertise.

If the patient can not be contacted, a next of kin or family member will be contacted. If not possible, the family physician will be contacted. If follow up is impossible, the investigators will contact the city hall and administrative service of his hometown to seek for possible death.

This reference methodology for outcome adjudication in PE studies has been used and described in all major diagnostic studies on PE ^{13,32,33,47}.

8 SPECIFIC RESEARCH COMMITTEES

8.1 Steering committee

Members of the committee: Dr Yonathan FREUND, Alexandra ROUSSEAU, Pr Bruno RIOU, Pr Tabassome SIMON; Pr Patrick RAY (Paris, France),

Missions: design the study, define target population, define primary and secondary assessment criteria, monitor inclusion rate and follow up of the patients.

8.2 Endpoint Adjudication Committee

Members of the committee: Pr Olivier HUGLI (Lausanne, Suisse), Pr Olivier SANCHEZ (Paris, France), Pr Yann-Eric CLAESSENS (Monaco, MC),

Missions: independently adjudicate the occurrence of likely thrombo-embolic event after 3 month follow up, in case of undocumented suspicion, or death.

Operating methods: For all patients that had an event during the 3 months follow up that could be related to a thrombo-embolic event, the medical record will be anonymised and blinded to the study period, and sent for external adjudication to the Endpoint Adjudication Committee. Cf 7.2

9 SAFETY ASSESSMENT - CLINICAL TRIAL RISKS AND REQUIREMENTS

9.1 Definitions

According to Article R1123-39 of the French Public Health Code :

Adverse event

Any untoward medical occurrence in a clinical trial subject and which does not necessarily have a causal relationship with the trial or the treatment administered in the trial.

Adverse drug reaction

Any adverse event likely to be related to the clinical trial.

Serious adverse event

Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is considered "medically significant".

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the current available information concerning the trial treatments or the trial procedures.

According to the notice to sponsors of clinical trials not conducted on medicinal products (ANSM):

New safety issue

Any new information regarding safety:

- that might significantly alter the assessment of the benefit-risk ratio of the trial
- or which might lead to modify the trial documents or alter the conduct of the trial.

Examples:

- a) any clinically significant increase in the frequency of an expected serious adverse reaction
- b) the premature termination or temporary interruption, of a trial conducted with the same experimental product (act or procedure) in another country, for safety reasons;

- c) recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the clinical trial subjects safety;
- d) suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is informed by the investigator, who also provides any follow-up reports

9.2 The investigator's roles

The investigator **should assess the seriousness of each adverse event** and report all serious and non-serious adverse events in the case report form (CRF)

9.2.1 Serious adverse events that require an immediate notification to the sponsor

According to the article R1123-54 of the French public health code, the investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except for those that are listed in the protocol (see. section 9.2.2.1) as not requiring immediate notification.

An adverse event is considered serious when one of the following criteria is fulfilled:

- 1- Death
- 2- Life-threatening event
- 3- Requiring hospitalization or prolonging hospitalization
- 4- Persistent or significant disability or incapacity
- 5- Congenital abnormality or birth defect
- 6- Or any other adverse event considered "medically significant"

For example : the investigator must immediately notify the sponsor any death due to any cause.

The investigator must report all SAE that occur in trial participants:

- * Starting from the subject informed consent form signature date
- * throughout the period during which the participant is followed-up (3 months), as required by the trial

The investigator must document the serious adverse event at the best and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events by using following general terms:

Mild: Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily life activities

Moderate: Event is sufficiently discomforting so as to limit or interfere with daily life activities; may require interventional treatment

Serious: Event results in significant symptoms that prevents normal daily life activities; may require hospitalization or invasive intervention

The investigator assesses the causal relationship between the serious adverse events and the trial procedure (group allocation).

9.2.2 Specific features of the protocol

The serious adverse events associated with specific trial procedures or exams, and which are expected, are:

thrombo-embolic event that were not diagnosed at ED inclusion visit.

9.2.2.1 Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events should be only recorded in the "adverse event" section of the case report form.

- Special circumstances
 - Hospitalization for a pre-existing condition
 - Hospitalization for a medical or surgical intervention planned before the enrolment in the trial
 - Return to the hospital for a medical consultation (for example in Cardiology department) if planned during the inclusion visit at ED
 - Return to the hospital for a medical consultation not planned during the inclusion visit at ED
 - Admission for social or regulatory reasons

- Serious adverse events which may occur during the patient's trial participation
 - Admission to an Emergency Department (ED) at inclusion
 - Requiring hospitalization immediately following the inclusion visit (ED visit)
 - Hospitalization for PE diagnosis
 - Hospitalization for other pathology (not related to PE or its complications) [for example: myocardial infarction, angina, pericarditis, cancer, etc.]

- Any new admission to ED or new hospitalization occurring during patient's trial participation after the 1st inclusion visit, except for a DVT or a PE and its complications

9.2.2.2 Adverse events that are "not serious" but which are significant for the safety of participants

These adverse events are "not serious" but they were considered as "serious" adverse event:

- Acute renal failure from contrast induced nephropathy
- Severe hemorrhage due to anticoagulation treatment

The investigator must notify the sponsor about these "not serious" adverse events, in accordance with the same procedures and deadlines as serious adverse events (see section 9.3). These events can be considered "medically significant".

9.3 Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE. The report must be signed by the investigator of the centre.

Each item in the form must be completed by the investigator so that the sponsor can perform the appropriate analysis of the event.

This initial notification must be followed by one or more detailed written follow-up report(s), signed by the investigator.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following information: research acronym, identification number and initials of the subject, nature and date of the serious adverse event.

Any adverse event will be monitored until its resolution (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The SAE initial notification, follow-up reports and all other documents must be sent to the sponsor via fax to the Vigilance Department at the following fax number: 01 44 84 17 99.

For studies using e-CRF:

- the investigator completes the SAE notification form in the e-CRF, and after validation, she/he prints the form out and signs it before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in Appendix 3. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator should answer to all sponsor queries to get additional information on the reported event.

For all questions relating to the notification of an adverse event, the investigator can contact the Vigilance department via email at the following email address: vigilance.drcd@drc.aphp.fr

9.3.1 The sponsor's roles

The sponsor, represented by its Vigilance department, continuously assesses the clinical trial safety throughout the research.

9.3.1.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- * the seriousness of all adverse events reported
- * the causal relationship of these events with each clinical trial procedure

All serious adverse events considered by the investigator and/or the sponsor as likely related to the clinical trial procedure are suspected adverse reactions.

- * the expected or unexpected nature of these adverse reactions

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the regulatory timelines, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the appropriate Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.
- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.
- The follow-up declaration must be made no later than 7 days after the 7- days deadline.

The sponsor must notify all investigators about any data that could affect the safety of the trial participants.

9.3.1.2 Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio of the trial, or which could lead to modify the conduct of the trial.

New facts must be declared to the competent authorities as soon as the sponsor is informed and no later than 7 calendar days of the sponsor becoming aware. Additional relevant information must be sent within additional 7 days from the receipt of follow up reports.

9.3.1.3 Annual safety report

Once a year for the whole duration of the clinical trial, the sponsor must prepare an annual safety report (ASR) which includes, in particular:

- an analysis of the safety profile of the trial
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the beginning of the research

The report must be provided no later than 60 days after the anniversary date on which the first patient has been enrolled in the trial.

9.4 Data Safety Monitoring Board

There will be no data safety monitoring board, as the research is at very low risk.

10 DATA MANAGEMENT

10.1 Data collection methods

Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-EST. Data will be completed by the investigators for each visit of follow up with the help of a Clinical Research Technician (CRT) of URC-Est for AP-HP centers and of each center for others centers.

After an eligible patient is screened and fulfil all inclusion criteria, and no non-inclusion ones, then his consent will be sought. When included, the physician in charge or the local investigator will record the following data on an eCRF.

A local research assistant can help the physician in charge to this task, either the same day, (or retrospectively the following days if some data were not recorded) under the control of the local investigator or the treating physician. He will then complete and record all mandatory data in an electronic CRF.

Outcome data recorded at follow up will be entered in the same eCRF, as any serious adverse events that might occur.

10.2 Identification of data collected directly in the CRFs and that will be considered as source data

For each recruited patient after randomization, besides usual clinical and biological data, we will collect the following specific items:

Both the Revised Geneva Score and Wells score at presentation.

Any return visit to the hospital or to a physician during the follow up

All imaging studies that the patient has undergone during the follow up

Any assessment of renal function during the follow up (creatinine level)

Intake of anticoagulant regimen

Bleeding/hemoraghe that requires withholding anticoagulant, antagonisation, or hospitalisation

10.3 Right to access source data and documents

10.3.1 Access to data

In accordance with GCPs:

- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor

- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.3.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

10.3.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown. The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

10.4 Data processing and storage of documents and data

10.4.1 Identification of the manager and the location(s) for data processing

Data entry will be carried out on electronic media via a web browser by the local research assistant or investigator (CleanWEB, Telemedicines Technologies).

10.4.2 Data processing (CNIL, the French Data Protection Authority) in France.

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de référence". The processing of personal data for this research falls under the scope of the provisions of Articles 53 to 61 of the Law of 6 January 1978 relating to information technology, data files and privacy, modified by Law No. 0204-801 of 6 August 2004.

10.4.3 Archival

Specific documents for biomedical research will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archival includes, in particular:

A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the research for the investigator

A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research for the sponsor

"Research" binders for the Investigator and the sponsor, including:

the successive versions of the protocol (identified by the version no. and date), and the appendices

the CPP favourable opinion

letters of correspondence

the inclusion list or register

the appendices specific to the research

the final research report

The data collection documents

10.5 Ownership of the data

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

11 STATISTICAL ASPECTS

11.1 Description of statistical methods to be used including the timetable for the planned interim analyses

No interim analysis is planned.

Baseline characteristics of patients will be described according to group of intervention. Continuous variables will be summarized using descriptive statistics, i.e number of subjects, mean, median, standard deviation (s.d), inter quartile range, minimum and maximum. Qualitative variables will be summarized by frequency and percentage.

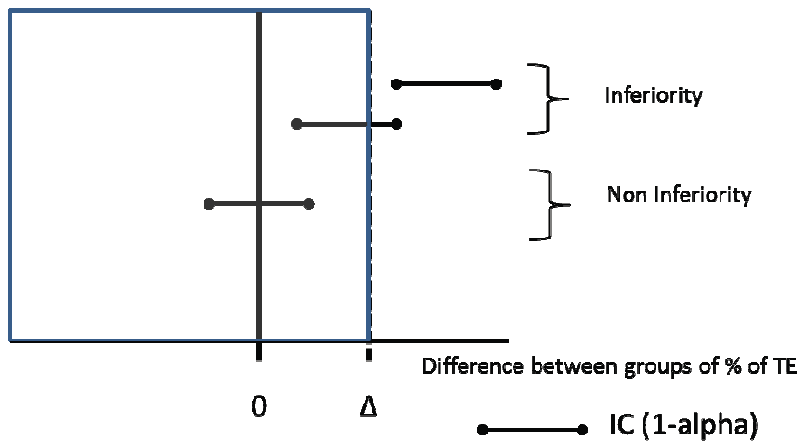
Principal criteria analysis:

Since this is a non inferiority study, analysis of the principal criterion will be performed on per protocol population. Secondary analysis will be performed on ITT population.

Thrombo-embolic event (TE event) will be defined by: DVT (assessed by proximal compression ultrasonography) or PE (a CTPA or angiography showing intraluminal defect, or a Ventilation/Perfusion lung scan showing a high-probability pattern)

The decision rule will be based on the upper bound of the 90% two sided confidence interval of the difference of percentage of TE events between groups.

If the upper bound of the confidence interval is above the 1.5% of difference, the non inferiority hypothesis of the intervention group will be rejected. Dunnett and Gent chisquare test will also be performed.



Secondary analysis will be performed on ITT population.

Considering cluster randomization, confirmatory analysis will be performed using generalized estimating equation (GEE) assuming an exchangeable correlation matrix structure and considering clustering at site level.

Secondary evaluation criteria

Secondary criteria will be compared under superiority hypothesis and on ITT population.

Descriptive analysis will be performed.

Superiority approach will be used to compare secondary evaluation criteria between groups.

The ED length stay and the mean of hospital admission following the ED visit will be compared using mixed model considering center as random effect.

Unnecessary irradiative imaging, adverse events and Deaths at 3 months will be compared using generalized estimating equation (GEE) assuming an exchangeable correlation matrix structure and considering clustering at site level.

11.2 Calculation hypotheses for the number of subjects required and the result

According to recent large European cohorts, we estimate that the rate of primary endpoint in our control group will be 1.5%^{32,33,48}.

To be regarded as non-inferior, the maximal difference in proportions between two groups (Delta) should not exceed 1.5% - an absolute rate of primary event of 3% in the intervention group. This failure rate corresponds to the upper bound of observed rate after a negative CPTA and is a widely accepted criterion for the validation of diagnostic strategies for PE⁴⁹. This rate is in line with previous landmark studies that comprise the basis of our current understanding.

Sample size under non inferiority hypothesis:

To assess non inferiority of the "PERC strategy", with alpha = 5%, beta=20%, one sided, N1= 1624 subjects are needed (East 6, Cytel).

Cluster design effect hypothesis:

15 clusters and 2 periods.

Intraclass correlation coefficient (CCIC)=0.002

Inter period correlation (η) = 0.001

Mean cluster size for one period (m)= 60 patients

Cluster design effect: $D = (1+(m-1) \times CCIC) - \eta = 1.12$

Sample size taking cluster design effect into account and 5 % of non-evaluable patients:

Sample size needed = $D \times N1 = 1911$ patients

With 15 clusters and 2 period /cluster, 64 subjects per cluster per period are required and will lead to 1920 subjects.

11.3 Anticipated level of statistical significance

Non inferiority analysis cf. above.

All superiority test will be performed at 5%.

11.4 Statistical criteria for termination of the research.

Not applicable

11.5 Method for taking into account missing, unused or invalid data

Missing data will not be replaced except for the principal criteria for the secondary ITT analysis. Missing value will be considered as an event whatever the group randomized.

11.6 Management of modifications made to the analysis plan for the initial strategy.

Modification made in analysis will be documented in the final report.

11.7 Selection of populations

Per protocol population: real strategy applied whatever the group allocated

ITT population: sites according to the randomized group even if the strategy allocated was not applied.

12 QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP.

12.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.

The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety and protection of the research subjects are met
- the data reported is exact, complete and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs and with the legislative and regulatory provisions in force

12.1.1 Strategy for opening the centres

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan.

12.1.2 Level of centre monitoring

In the case of this research, which is considered **A** risk, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level **A**

12.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein

12.3 Case Report Form

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.

This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCD's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCD for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

12.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

12.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

13 ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for obtaining information and consent from research participants

After a screened patient is confirmed to be eligible for recruitment, the treating physician or the local investigator will explain the rationale and objectives of the study. Only the participant will be able to sign the informed consent. An information sheet will be given to him, and he will be able to discuss the study with the physician or local investigator or research assistant. The patient will be notified his allocation group and its implication. To be recruited, the patient will have to sign the informed consent before venupuncture for D-dimer testing (for control group or PERC positive patients) or before ED discharge (for experimental group for PERC negative patients)

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The subject will be granted a reflection period, running from the time when the subject receives the information and the time when he or she signs the consent form.

The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the research, i.e. before venupuncture for D-dimer testing (for control group or PERC positive patients) or before ED discharge (for experimental group for PERC negative patients)

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the subject's consent form.

13.2 Subject prohibited from participating in another research or an exclusion period anticipated after the research, if applicable

The exclusion period specified for this is 3 months after inclusion

During his participation to Proper study, the subject may not participate in other interventional studies.

13.3 Compensation for subjects

No compensation is anticipated for the patients as compensation for the inconveniences relating to the research.

13.4 Legal obligations

13.4.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Development Department (DRCD) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time

for medical or administrative reasons. In this case, notification will be sent to the investigator.

13.4.2 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

AP-HP, as sponsor, obtains for this biomedical research prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

13.4.3 Request for authorization from the ANSM

AP-HP, as sponsor, obtains for this biomedical research prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

13.4.4 Commitment to compliance with the MR 001 "Méthodologie de Reference"

AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

13.4.5 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.

The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

13.4.6 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

14 FUNDING AND INSURANCE

14.1 Funding source

This study is funded by the Projet Hospitalier de Recherche Clinique.

14.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Assistance Publique- Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

15 PUBLICATION RULES

15.1 Author list

Author list for the main article of the PROPER study will be as follows:

Yonathan Freund, Alexandra Rousseau, Inv1, Inv2 ..., Patrick Ray, Yann-Erick Claessens, Olivier Hugli, Olivier Sanchez, Tabassome Simon, Bruno Riou.

"Inv" standing for each local investigator of a center that included at least 100 patients during the study.

15.2 Mention of the affiliation of AP-HP for projects sponsored or managed by AP-HP

Affiliation of authors from Assistance Publique – Hôpitaux de Paris will include "AP-HP, hospital, department, city, postcode, France"

15.3 Mention of the AP-HP manager (DRCD) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Département de la Recherche Clinique et du Développement, Clinical Research and Development Department)"

URC-Est and CRC -Est will be thanked for their logistical support in the "Acknowledgment"

15.4 Mention of the financier in the acknowledgements of the text

The manuscript will include the following statement:
“The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2014 (Ministère de la Santé)”

This research has been registered on the website <http://clinicaltrials.gov/> under number registration number NCT 02375919.

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17 LIST OF ADDENDA

17.1 Appendix 1: Pre test clinical probability of PE

Simplified Revised Geneva Score :

Age > 65 years	1
Previous DVT or PE	1
Surgery or fracture within 1 month	1
Active malignant condition	1
Unilateral lower limb pain	1
Hemoptysis	1
Heart Rate	
75 – 94 beats per min	1
>94 beats per min	2
Pain on lower limb deep venous palpation and unilateral edema	1

low: 0-1; intermediate: 2-4; high: >4

Wells Score:

Clinical signs and symptoms of DVT	3
Immobilization or surgery within 4 weeks	1.5
Heart rate > 100 beats per min	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Malignancy	1
Alternative diagnosis is less likely than PE	3

Low: 0-1; intermediate: 2-6; high: >6

Gestalt:

The gestalt is an unstructured estimation of the clinical probability of having a PE, assessed empirically by the physician in charge.

As described in previous studies ^{1,30}, this assessment is established as the answer of the question “How do you estimate the pre-test clinical probability: low, moderate, or high? ¹⁰”

17.2 Appendix 2: List of Investigators

		Name	first name	Town	Country
1	Pitié-Salpêtrière	Freund	Yonathan	Paris	France
2	Tenon	Ray	Patrick	Paris	France
3	Saint-Antoine	Pateron	Dominique	Paris	France
4	Bichat	Choquet	Christophe	Paris	France
5	Lariboisière	Truchot	Jennifer	Paris	France
6	HEGP	Feral-Pierssens	Anne-Laure	Paris	France
7	Cochin	Doumenc	Benoit	Paris	France
8	Ambroise Paré	Beaune	Sebastien	Boulogne	France
9	Henri Mondor	Khellaf	Mehdi	Créteil	France
10	Rangueil	Charpentier	Sandrine	Toulouse	France
11	Edouard Herriot	Tazarourte	Karim	Lyon	France
12	CHRU Besançon	Desmettre	Thibaut	Besançon	France
13	Saint Camille	Wargon	Matthias	Bry s Marne	France
14	Avicennes	Adnet	Frederic	Bobigny	France
15	CHU Rouen	Joly	Luc-Marie	Rouen	France

17.3 Appendix 3: SAE form

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)		PARTIE RESERVEE AU PROMOTEUR - - DRRC 20 - - - -
	Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une Recherche Biomédicale ne portant pas sur un produit de santé	

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99
Se référer à la grille de notification des EIG en vigueur

1. Identification de la recherche Acronyme : Proper Code de la Recherche : P 140913 Autre référence : IDRCB 2015-A00215-44		Notification initiale <input type="checkbox"/> Suivi d'EIG <input type="checkbox"/> N° du suivi _ _ _
Titre complet de la Recherche Biomédicale: Score PERC pour exclure le diagnostic d'Embolie Pulmonaire aux urgences chez des patients de faible risque. Essai randomisé, contrôlé de non infériorité. (Etude Proper)		Date de notification : _ _ _ _ 2_ 0_ _ jj mm aaaa Date de prise de connaissance de l'EIG par l'investigateur : _ _ _ _ 2_ 0_ _ jj mm aaaa
		Risque : <input checked="" type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/> D Plan expérimental : <input type="checkbox"/> Essai non comparatif <input checked="" type="checkbox"/> Essai comparatif : <input type="checkbox"/> Double aveugle <input type="checkbox"/> Simple aveugle <input checked="" type="checkbox"/> Ouvert <input checked="" type="checkbox"/> Randomisé (par centre) <input type="checkbox"/> Non randomisé

2. Centre Investigateur Nom de l'établissement : _____ Ville et code postal : _____ Service : _____		Investigateur (nom/prénom) : _____ Tél : _____ Fax : _____
--	--	--

3. Identification et antécédents de la personne se prêtant à la recherche Référence de la personne : _ _ _ _ - _ _ _ _ - _ _ _ _ <small>n°centre - n° ordre de sélection - initiale - initiale nom - prénom</small>		Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH le cas échéant) : _____ _____ _____ _____
Sexe : <input type="checkbox"/> M <input type="checkbox"/> F Poids : _ _ _ kg Taille : _ _ _ cm	Date de naissance : _ _ _ _ _ _ _ _ jj mm aaaa Age : _ _ _ ans	
Date de signature du consentement : _ _ _ _ 2_ 0_ _ jj mm aaaa		
Date de randomisation : _ _ _ _ 2_ 0_ _ jj mm aaaa		

4. Procédures et actes ajoutés par la recherche (ex. : biopsies, IRM ... Barrer l'encadré si procédures et actes non réalisés) :	Date de réalisation (jj/mm/aaaa)	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Score PERC	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	<input type="checkbox"/>
_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	<input type="checkbox"/>
_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	<input type="checkbox"/>
_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	<input type="checkbox"/>
_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	<input type="checkbox"/>

5. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'évènement indésirable (compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants → Annexe jointe au présent formulaire : <input type="checkbox"/> Oui <input type="checkbox"/> Non ou barrer l'encadré si non applicable) :						
Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie ⁽¹⁾	Posologie / jour	Date de début (jj/mm/aaaa)	En cours ⁽²⁾	Date de fin (jj/mm/aaaa)
_____	_____	_____	_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	_ _ _ _ 2_ 0_ _
_____	_____	_____	_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	_ _ _ _ 2_ 0_ _
_____	_____	_____	_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	_ _ _ _ 2_ 0_ _
_____	_____	_____	_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	_ _ _ _ 2_ 0_ _
_____	_____	_____	_____	_ _ _ _ 2_ 0_ _	<input type="checkbox"/>	_ _ _ _ 2_ 0_ _

(1) Voie d'administration : VO=voie orale ; IM=intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG
 14YFD-PROPER_FormulaireEIG_V2_20150605_DRCD VIG_FormulaireEIG-HP3_V3_20131126_CB5 1/3

Acronyme Proper Référence de la personne se prêtant à la recherche : _ _ _ _ - _ _ _ _ - _ _ - _ _ <small style="display: flex; justify-content: space-between; font-size: 8px;"> n°centre n°ordre de sélection initiale nom prénom </small>		PARTIE RESERVEE AU PROMOTEUR - DRRC 20 -
6. Evènement indésirable grave [EIG]		
Diagnostic : <input type="checkbox"/> Définitif <input type="checkbox"/> Provisoire _____ _____	Organe(s) concerné(s) : _____ _____	Symptôme(s) : _____ _____
Date de survenue des premiers symptômes : _ _ / _ _ / _ 2 _ 0 _ _ Préciser lesquels : _____ _____		_____ _____
Date d'apparition de l'EIG : _ _ / _ _ / _ 2 _ 0 _ _ jj mm aaaa Heure de survenue : _ _ : _ _ hh _ _ min <input type="checkbox"/> donnée manquante	Délai entre la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG : _ _ / _ _ / _ _ jj hh min	Critères de gravité : <input type="checkbox"/> Nécessite ou prolonge l'hospitalisation : du _ _ / _ _ / _ 2 _ 0 _ _ au _ _ / _ _ / _ 2 _ 0 _ _ <input type="checkbox"/> en cours <input type="checkbox"/> Décès <input type="checkbox"/> Mise en jeu du pronostic vital <input type="checkbox"/> Incapacité ou handicap important ou durable <input type="checkbox"/> Anomalie ou malformation congénitale <input type="checkbox"/> Autre(s) critère(s) médicalement significatif(s), préciser : _____ _____ _____
L'évènement a-t-il conduit à une interruption de la procédure/acte ajouté par la recherche ? <input type="checkbox"/> Non <input type="checkbox"/> Oui Date : _ _ / _ _ / _ 2 _ 0 _ _ L'arrêt de la procédure/acte ajouté par la recherche a été : <input type="radio"/> Provisoire <input type="radio"/> Définitif Le cas échéant, date de reprise de la procédure/acte ajouté par la recherche : _ _ / _ _ / _ 2 _ 0 _ _ Récidive de l'EIG après reprise de la procédure/acte ajouté par la recherche : <input type="radio"/> Non <input type="radio"/> Oui - Date : _ _ / _ _ / _ 2 _ 0 _ _		_____ _____ _____
Evénements d'intérêt particulier : <input type="checkbox"/> Hémorragie sévère due aux anticoagulants <input type="checkbox"/> Insuffisance rénale aigüe due à une néphropathie induite par les produits de contraste <input type="checkbox"/> Evénements thromboemboliques non diagnostiqués à la visite initiale pour les patients randomisés dans le groupe expérimental <input type="checkbox"/> Nouvelle consultation aux urgences ou à l'hôpital pour les patients randomisés dans le groupe expérimental		Degré de sévérité : <input type="checkbox"/> Léger <input type="checkbox"/> Modéré <input type="checkbox"/> Sévère
Evolution de l'évènement		
<input type="checkbox"/> Décès <input type="radio"/> sans relation avec l'EIG <input type="radio"/> en relation avec l'EIG Date : _ _ / _ _ / _ 2 _ 0 _ _ jj mm aaaa	<input type="checkbox"/> Sujet non encore rétabli, préciser : <input type="radio"/> Etat stable <input type="radio"/> Aggravation <input type="radio"/> Amélioration	
<input type="checkbox"/> Guérison : <input type="radio"/> sans séquelles <input type="radio"/> avec séquelles, préciser lesquelles : _____ _____ _____	Date : _ _ / _ _ / _ 2 _ 0 _ _ jj mm aaaa _ _ : _ _ hh min	Des mesures symptomatiques ont été prises : <input type="checkbox"/> Non <input type="checkbox"/> Oui Si oui, préciser : _____ _____ _____
7. Autre(s) étiologie(s) envisagée(s) :		
<input type="checkbox"/> Non <input type="checkbox"/> Oui Si oui, préciser : _____ _____ _____		
8. Examen(s) complémentaire(s) réalisé(s) :		
<input type="checkbox"/> Non <input type="checkbox"/> Oui Si oui, préciser date, nature et résultats : [joindre les bilans] _____ _____ _____		

9. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles) :		
<p>Lié à la recherche biomédicale :</p> <p><input type="checkbox"/> Oui : <input type="radio"/> à la procédure/acte de la recherche biomédicale :</p> <p style="margin-left: 40px;"><input type="checkbox"/> faux négatif de la règle PERC <input type="checkbox"/> Relation certaine <input type="checkbox"/> Relation probable <input type="checkbox"/> Relation possible <input type="checkbox"/> Relation improbable</p> <p><input type="checkbox"/> Non : <input type="radio"/> à la progression de la maladie faisant l'objet de la recherche : (à compléter)</p> <p><input type="radio"/> à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : _____</p> <p style="margin-left: 40px;"><input type="checkbox"/> traitements anticoagulants</p> <p style="margin-left: 40px;"><input type="checkbox"/> produit de contraste administré lors de la réalisation de l'angiographie pulmonaire</p> <p><input type="radio"/> à une maladie intercurrente, laquelle : _____</p> <p><input type="radio"/> autre, préciser : _____</p>		
Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	

PHRC-14-0355_APHP_Freund

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS	Partie réservée au promoteur -- - DRRC 20 -- -
	Liste relative aux médicaments concomitants utilisés dans le cadre d'une recherche biomédicale : Annexe au formulaire de notification d'un Evènement Indésirable Grave (EIG)	

Dès la prise de connaissance de l'EIG par l'investigateur, ce document doit être dûment complété, signé et retourné **sans délai** au pôle Vigilance du DRCD-Siège par **télécopie** au +33 (0)1 44 84 17 99 avec le formulaire de notification d'EIG complété

Notification initiale Suivi d'EIG N° du suivi | _ | _ |

Acronyme: Proper	Investigateur (nom/prénom) : _____
Référence de la personne se prêtant à la recherche : _ _ _ _ - _ _ _ _ _ - _ _ - _ _ <small>n°centre - n° ordre de sélection - initiale - initiale nom - prénom</small>	Service : _____ Tél. : _____ Fax : _____

REPORTER TOUS LES MEDICAMENTS CONCOMITANTS AU MOMENT DE L'EIG, A L'EXCLUSION DE CEUX UTILISES POUR TRAITER L'EVENEMENT INDESIRABLE :						
Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie ⁽¹⁾	Posologie / jour	Date de début (jj/mm/aaaa)	En cours ⁽²⁾	Date de fin (jj/mm/aaaa)
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _
_____	_____	_____	_____	_ _ _ _ _ _ _ _ _	<input type="checkbox"/>	_ _ _ _ _ _ _ _ _ 2 1 0 _ _

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	