

# 1 ANTICOVID Trial Protocol

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**2 First version of Protocol**

Research code number: APHP201624

Title: “ANTIcoagulation in severe COVID-19 patients: a multicenter, parallel-group, open-label, randomised controlled trial”

ANTICOVID

Version no. 1.1 dated: 22 / 03 / 2021

The study will be carried out in accordance with the protocol, with current good practices, and with statutory and regulatory requirements.

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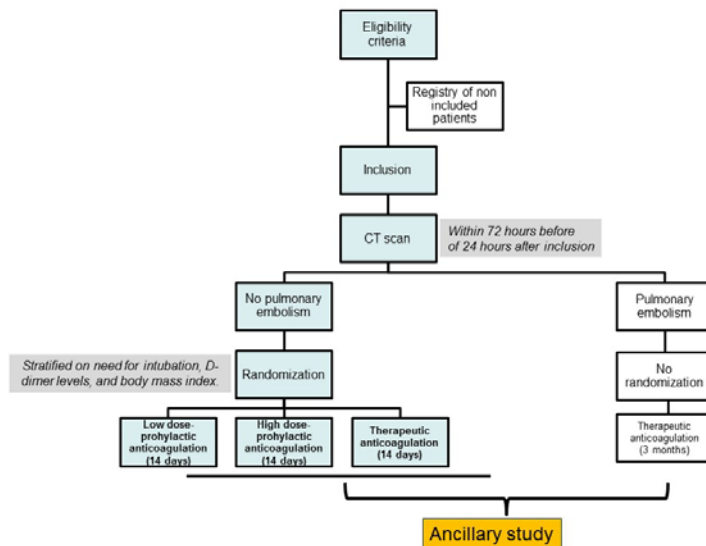
## 1 SUMMARY

Full title	ANTIcoagulation in severe COVID-19 patients: a multicentre, parallel-group, open-label, randomised controlled trial
Acronym/reference	ANTICOVID
Coordinating investigator	Dr Vincent LABBE
Scientific Director	Pr Armand MEKONTSO-DESSAP
Sponsor	AP-HP
Scientific justification	<p>Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease <sup>1</sup> due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality <sup>2-4</sup>.</p> <p>The incidence of macrovascular thrombotic events varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of arterial or vein thrombosis captured and severity of illness <sup>2-4</sup>. In a cohort of 144 critically ill patients, Al-Samkari et al. reported a 18% (95% CI, 12.1-25.3) rate of overall macrovascular thrombotic events <sup>4</sup>. Based on these observational results in patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several institutions have recently released guidance statement to prevent macrovascular thrombotic events with dose escalation anticoagulation <sup>5,6</sup>. In these recommendations, high-dose prophylactic anticoagulation (HD-PA) and therapeutic anticoagulation (TA) can be employed either empirically or based on the body mass index and increased D-dimer values <sup>5-7</sup>. No randomized trial has validated this approach, and other recent recommendations challenge this approach <sup>6,8</sup>.</p> <p>Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even in the absence of obvious macrovascular thrombotic events. A large review of autopsy findings in COVID-19-related deaths reported micro thrombi in small pulmonary vessels <sup>9</sup>. More generally, COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs lead to widespread microvascular thrombosis with microangiopathy and occlusion of capillaries <sup>2,10,11</sup>. Thus, in severe COVID-19 patients requiring oxygen therapy without initial macrovascular thrombotic event, a HD-PA or a TA could be beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and</p>

	<p>multi-organ microcirculatory dysfunction. In a large observational cohort of 2,773 COVID-19 patients, Paranjpe et al. found a lower in-hospital mortality in ventilated patients receiving TA as compared to those receiving PA (29.1% vs. 62.7%). In a multivariable proportional hazards model, a longer duration of TA was associated with a reduced risk of mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89; p&lt;0.001) <sup>12</sup>. Similar findings were recently reported by Jonmarker et al <sup>13</sup>.</p> <p>To date, no randomized clinical trial has evaluated the best anticoagulation strategy in COVID-19 patients, especially those in whom pulmonary embolism has been excluded on the chest computed tomography with pulmonary angiogram (CTPA). It seems important to rationalize and compare anticoagulation strategies in this context. Our hypothesis is dual: i) first, that TA and HD-PA strategies mitigate microthrombosis and each limit the progression of COVID-19, including respiratory failure and multi-organ dysfunction, with in fine a decreased mortality and duration of disease, as compared to a low-dose PA; ii) second, that TA outperforms HD-PA in this setting.</p>
Main objective and primary endpoint	<p>The main objective is to compare the efficacy of three <u>strategies</u> (LD- PA, HD-PA, and TA) to reduce the mortality and the time to clinical improvement in patients with COVID-19 pneumonia and free from pulmonary embolism at inclusion. Patients with pulmonary embolism at inclusion will not be randomized; they will receive TA as recommended and will be followed up (see ancillary study).</p> <p>The primary endpoint is a hierarchical criterion assessed at 28 days, including all-cause mortality, followed by the time to clinical improvement according to the Finkelstein–Schoenfeld method.</p> <p>This method is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion, using all-cause mortality, followed by the time to clinical improvement when patients cannot be differentiated on the basis of mortality. This method gives a higher importance to all-cause mortality.</p> <p>The time (number of days) to clinical improvement is defined as the time from randomization to an improvement of at least two points (from the status at randomization), using a seven-category ordinal scale derived a WHO recommended instrument <sup>14</sup>, as proposed by Coa et al <sup>15</sup>, using the following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized, requiring supplemental oxygen; 5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6. hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 7. death.</p> <p>The weaning of ventilation and of supplemental oxygen will be</p>

	protocolized.
Secondary objectives and endpoints	<p>The secondary objectives are to compare the benefit and risks of the three strategies (LD-PA, HD-PA, and TA) regarding:</p> <ol style="list-style-type: none"> <li>1. Mortality, morbidity and organ dysfunction; <ul style="list-style-type: none"> <li>- Score on WHO Ordinal Scale and seven category ordinal scale at Day-28;</li> <li>- Number of days alive and free from supplemental oxygen at Day-28;</li> <li>- Proportion of patients needing intubation at Day-28;</li> <li>- Number of days alive and free from invasive mechanical ventilation at Day-28;</li> <li>- Number of days alive and free from vasopressors at Day-28;</li> <li>- Length of intensive care unit stay;</li> <li>- Length of hospital stay;</li> <li>- Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L);</li> <li>- All-cause deaths at Day-28 and Day-90.</li> </ul> </li> <li>2. Efficacy on thrombotic events <ul style="list-style-type: none"> <li>- Proportion of patients with at least one macrothrombotic event including ischemic stroke, non-cerebrovascular arterial thrombotic event, deep venous thrombosis, pulmonary embolism, or central venous catheter-related deep venous thrombosis;</li> <li>- D-dimers and Sepsis-Induced Coagulopathy Score (SCS) at Day-7.</li> </ul> </li> <li>3. Tolerance of anticoagulation <ul style="list-style-type: none"> <li>- Proportion of patients with at least one major bleeding event (MBE) at Day-28;</li> <li>- Proportion of patients with at least one life-threatening bleeding event at Day-28;</li> <li>- Proportion of patients with any bleeding event at Day-28</li> <li>- Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28.</li> </ul> </li> </ol> <p>An ancillary study will assess clinical and biological characteristics of severe COVID-19 pneumonia with or without pulmonary embolism to establish a scoring system for COVID-19 related pulmonary embolism diagnosis.</p>
Design of the study	Multicenter open-label randomized controlled superiority trial aiming to compare LD-PA, HD-PA, and TA strategies, with a 1:1:1 ratio.
Population of study participants	Adult patients with oxygen dependent COVID-19 pneumonia.
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Age <math>\geq</math> 18 years;</li> <li>2. Severe COVID-19 pneumonia, defined by: i) a newly-appeared pulmonary parenchymal infiltrate; and ii) a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2); and iii) WHO ordinal scale <math>\geq</math> 5;</li> <li>3. Written informed consent (patient, next of skin or emergency</li> </ol>

	<p>situation).</p> <p>In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion for inclusion.</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Pregnancy and breast feeding woman;</li> <li>2. Postpartum (6 weeks);</li> <li>3. Extreme weights (&lt;40 kg or &gt;100 kg);</li> <li>4. Patients admitted since more than 72 hours to the hospital (if the WHO ordinal scale is 5 at time of inclusion) or since more than 72 hours to the intensive care unit (if the WHO ordinal scale is 6 or more at time of inclusion);</li> <li>5. Need for therapeutic anticoagulation;</li> <li>6. Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding</li> <li>7. Platelet count &lt; 50 G/L;</li> <li>8. Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;</li> <li>9. Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;</li> <li>10. Severe renal failure (creatinine clearance &lt;30 mL/min);</li> <li>11. Iodine allergy;</li> <li>12. Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;</li> <li>13. History of type II heparin-induced thrombocytopenia;</li> <li>14. Chronic oxygen supplementation;</li> <li>15. Moribund patient or death expected from underlying disease during the current admission;</li> <li>16. Patient deprived of liberty and persons subject to institutional psychiatric care;</li> <li>17. Patients under guardianship or curatorship;</li> <li>18. Participation to another interventional research on anticoagulation.</li> </ol>
Interventions or product under investigation	<p>All consecutive adult patients with oxygen dependent COVID-19 pneumonia will be included in the absence of exclusion criteria. A CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion:</p> <ul style="list-style-type: none"> <li>- If the CTPA is positive (pulmonary artery thrombosis), the patient will not be randomized and will receive TA according to the recommendations for thromboembolic disease.</li> <li>- If the CTPA is negative, the patient will be randomized to receive either LD-PA, HD-PA or TA, for 14 days (or until hospital discharge or weaning of supplemental oxygen during 48 consecutive hours, whichever comes first).</li> </ul>



Randomization will be stratified on the following criteria: center, need for intubation (yes or no), D-dimer levels (upper or lower than 3 µg/ml), and body mass index (upper or lower than 30 kg/m<sup>2</sup>).

Participants randomized to the LD-PA, HD-PA and TA strategies will receive the low weight molecular heparin (LMWH) tinzaparin, considering its contraindications, recommended dose ranges and monitoring if applicable, as follows: LD-PA : 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h. If tinzaparin is not punctually available, the use of enoxaparin will be allowed as follows: LD-PA: 4000 IU/24h; HD-PA: 4000 IU/12h; TA: 100 IU/kg/12h. The choice of tinzaparin as first line LMWH is driven by the following arguments: i) it is used in routine care; ii) the single daily dose facilitates its use in the clinical practice. In the case of renal failure (creatinine clearance < 30 mL/min) occurring after randomization or in case of invasive procedure at high risk of bleeding, LMWH may be replaced by a continuous intravenous infusion of unfractionated heparin as follows : LD-PA: 100 IU/kg/24h; HD-PA: 200 IU/kg/24h; TA: 500 IU/kg/24h, adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per the recommendations.

After day-14, or hospital discharge, or in case of an indication for TA, or in case of serious adverse event related to anticoagulation, the investigational anticoagulation strategy will be discontinued and anticoagulation treatment will be left at the discretion of attending physicians.

In all groups, recommendations for the management of COVID-19 pneumonia will be followed, including the use of dexamethasone. These recommendations will be subject to modifications based on the new literature data.



	Evaluation criteria will be collected at hospital discharge or at Day-28, and Day-90. The vital status may be obtained by phone call at Day-28 (if the patient has been discharged before Day-28) and at Day-90.
Other interventions added by the study	Interventions added by the study include a phone call at Day-28 and Day-90, unless the patient is still hospitalized. No invasive act will be added by the research.
Expected benefits for the participants and for society	COVID-19 is a critical situation during which the occurrence of macrovascular and microvascular thrombosis is particularly frequent and serious. Anticoagulation is a specific management strategy for thrombosis whose modalities are debated, with major heterogeneities of practices. We propose a randomized trial to rationalize and compare three anticoagulation strategies (LD-PA, HD-PA, and TA) in this context. The results of this trial, in the case our hypothesis is confirmed, will contribute to improve the management of COVID-19 patients with ultimately a potential decrease in the mortality and the time to clinical improvement.
Minimal risks and burden added by the study	No specific risk is added by the study; the three studied strategies are currently employed in COVID-19 patients with pneumonia requiring oxygen therapy as part of routine care.
Scope of the study	Anticoagulation in COVID-19 patients.
Number of participants included	Using estimates derived from the prior observational studies, a sample of at least 300 patients (100 per group) was estimated to provide $\geq 80\%$ power to detect a significant difference in the primary ranked composite outcome with 2-sided alpha of 0.05. Sample size calculations assumed 28-day mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/- 3 days, 14 days and 12 days, with LD-PA, HD-PA, and TA, respectively. We hypothesize a 15% rate of positive CTPA <sup>16,17</sup> . In order to randomize 300 patients, we aim at including 353 patients.
Number of centres	24
Schedule for the study	<ul style="list-style-type: none"> <li>- Inclusion period: 6 months</li> <li>- Participation period (treatment + follow-up): 90 days</li> <li>- Total duration: 9 months</li> </ul>
Number of enrolments expected per site and per month	2 to 3
Statistical analysis	No interim analysis is planned. Principal analysis will be performed according to intention to treat principle. The prespecified primary end point will be a ranked composite score that incorporates death and the time to clinical improvement, calculated in such manner that death constitutes a worse outcome than more days to reach clinical improvement.

	<p>Each patient will be compared with every other patient in the study and assigned a score (tie: 0, win: +1, loss: -1) for each pairwise comparison based on whom fared better. If one patient survived and the other did not, scores of +1 and -1 will be assigned, respectively, for that pairwise comparison. If both patients in the pairwise comparison survived, the assigned score will depend on which patient had more days to clinical improvement: the patient with fewer days will receive a score of +1, while the patient with more days will receive a score of -1. If both patients survived and had the same number of days to clinical improvement, or if both patients died, they both will be assigned a score of 0 for that pairwise comparison. For each patient, scores for all pairwise comparisons will be summed, resulting in a cumulative score for each patient. These cumulative scores will be ranked and compared between treatment groups via the Mann-Whitney technique.</p>
Funding sources	Leo Pharma

39 **2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH**

## 40 2.1.1 About the condition under investigation

41 Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory  
42 syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease<sup>1</sup> due to a state of  
43 profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and  
44 increased mortality<sup>2-4</sup>.

45 The incidence of macrovascular thrombotic event varies from 10 to 30% in COVID-19 hospitalized  
46 patients depending on the type of arterial or vein thrombosis captured and severity of illness<sup>2-4</sup>. In a cohort  
47 of 144 critically ill patients, Al-Samkari et al. reported a 18% (95% CI, 12.1-25.3) rate of overall  
48 macrovascular thrombotic event<sup>4</sup>. Recently, Suh et al. conducted a large review including 27 observational  
49 studies and 3342 patients with COVID-19. The authors report a pulmonary embolism incidence rate of  
50 14.8% (95% CI: 8.5, 24.5; I2 = 0.94) despite prophylactic anticoagulation (PA) (24). Based on these  
51 observational results in patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several  
52 institutions have recently released guidance statement to prevent macrovascular thrombotic event with  
53 dose escalation anticoagulation including a high dose-preventive anticoagulation (HD-PA) or a therapeutic  
54 anticoagulation (TA)<sup>5-7</sup>. No randomized trial has validated this approach, and other recent  
55 recommendations challenge this approach<sup>6,8</sup>.

56 Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even  
57 in the absence of obvious macrovascular thrombotic event. A large review of autopsy findings in COVID-  
58 19-related death reported micro thrombi in small pulmonary vessels<sup>9</sup>. More generally, COVID-19-induced  
59 endothelitis and coagulopathy across vascular beds of different organs lead to widespread microvascular  
60 thrombosis with microangiopathy and occlusion of capillaries<sup>2,10,11</sup>. Thus, in severe COVID-19 patients  
61 requiring oxygen therapy without initial macrovascular thrombotic event, a HD-PA or a TA could be  
62 beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and multi-  
63 organ microcirculatory dysfunction. In a large observational cohort of 2,773 COVID-19 patients, Paranjpe  
64 et al. found a lower in-hospital mortality in ventilated patients receiving TA as compared to those receiving  
65 PA (29.1% vs. 62.7%). In a multivariable proportional hazards model, a longer duration of TA was  
66 associated with a reduced risk of mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89; p<0.001)<sup>12</sup>.  
67 Similar findings were recently reported by Jonmarker et al<sup>13</sup>.

## 68 2.1.2 Usual practice about anticoagulation strategies in patients with severe COVID-19

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70 Based on observational studies of thrombotic risk, the « Groupe français d'étude pour l'hémostase et la  
71 thrombose (GFHT) » and the « Groupe d'intérêt en hémostase péri-opératoire (GIHP) » recommended  
72 three strategies of anticoagulation with dose escalation (LD-PA, HD-PA, and TA) depending on the  
73 thrombotic risk level<sup>7</sup> as assessed by: i) the severity of COVID-19; ii) the body mass index; iii) the known  
74 thrombotic risk factor (e.g., active cancer); iv) a severe inflammatory syndrome (e.g., fibrinogen > 8 g/L)  
75 or hypercoagulability (e.g., D-dimer > 3000 ng/mL) (**Annex 1**).

76 While acknowledging that a variety of anticoagulation strategies (LD-PA, HD-PA and TA) are currently  
77 used in routine practice for severe COVID-19, a group of French and European scientific societies<sup>6,8</sup>  
78 indicated that the optimal dosing in patients with severe COVID-19 remains unknown and warrants further  
79 prospective investigations. Moreover, they acknowledged the difficulty to evaluate the specific thrombotic  
80 risk for each patient, even with the use of D-dimers, whose thresholds are not consensual<sup>8</sup>.

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82 Current practices for the management of thrombotic risk in patients with severe COVID-19 are very  
83 heterogeneous. **Annex 2** presents the main observational studies reporting the strategies of anticoagulation  
84 used in usual practice in hospitalized patients with COVID-19. Three usual strategies are identified:

85 - A TA is used in one third of patients;

86 - A PA is used in two-thirds of patients. The dose (“low” or “high”) of PA is not always reported.

87 Jonmarker et al. reported in 152 intensive care unit patients the use of LD-PA and HD-PA in 44% and 32%  
88 of patients, respectively. The TA was administrated in 24% of patients in that study <sup>13</sup>.

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90 2.1.3 Current randomized clinical trials

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92 Several trials are studying various doses for anticoagulation strategy in COVID-19 patients <sup>8</sup>.

93 In the Iranian INSPIRATION trial recently published online in JAMA on March 18, 2021 <sup>18</sup>, Sadeghipour  
94 et al. compared the efficacy of a standard low dose prophylactic anticoagulation (40 mg once daily  
95 enoxaparin) with a weight-based high dose prophylactic anticoagulation (1 mg/kg enoxaparin) among  
96 severe COVID-19 patients admitted to intensive care unit. High dose prophylactic anticoagulation did not  
97 result in a significant difference in the primary outcome (a composite of adjudicated venous or arterial  
98 thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days), as  
99 compared with standard-dose prophylactic anticoagulation. The risk of bleeding was also similar between  
100 the two groups. In addition, the others main trials (in progress, not published) are the French COVIDOSE  
101 trial, as well as 3 international trials of similar design from the REMAPCAP, ACTIV-4, and ATTACC  
102 platforms.

103 However, **the ANTICOVID study differs** from all these studies for at least three methodological and  
104 clinical reasons, as detailed below.

105 Firstly, the inclusion criteria differ because of systematic (ANTICOVID) vs. non-systematic  
106 (INSPIRATION, COVIDOSE, REMAPCAP, ACTIV-4, ATTACC) investigation of macro-thrombosis,  
107 which is de facto an indication for curative anticoagulation. ANTICOVID excludes macrothrombosis from  
108 randomization (chest computed tomography with pulmonary angiogram before randomization to exclude  
109 pulmonary embolism) and will provide an answer to the specific question of micro thrombosis.  
110 Microvascular arterial and venous thrombotic events are a major concern in critically ill patients with  
111 COVID-19, even in the absence of obvious macrovascular thrombotic events. A large review of autopsy  
112 findings in COVID-19-related death reported micro thrombi in small pulmonary vessels <sup>9</sup>. More generally,  
113 COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs leads to  
114 widespread microvascular thrombosis with microangiopathy and occlusion of capillaries <sup>2,10,11</sup>, which may  
115 ultimately contribute to organ failure. In this respect, the ANTICOVID study is complementary of other  
116 studies.

117 On the other hand, in contrast to these 5 other trials, ANTICOVID explicitly excludes patients with a  
118 higher risk of bleeding (e.g., extreme weight, renal failure with creatinine clearance < 30 ml/min). Indeed,  
119 renal failure has been shown to be an independent risk factor for bleeding in critically ill patients requiring  
120 curative anticoagulation <sup>19</sup>. In addition, in patients with acute renal failure after ANTICOVID  
121 randomization (or in patients undergoing invasive procedures with bleeding risk), low weight molecular  
122 heparin may be replaced by a continuous intravenous infusion of unfractionated heparin, in order to

123 minimize the risk of bleeding. Therefore, ANTICOVID will allow evaluation of anticoagulation dose  
 124 escalation in a population with a minimized baseline bleeding risk.

125 Secondly, the anticoagulation strategies studied in the 5 trials are different from ANTICOVID (Table 1).

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127 **Table 1: Anticoagulation strategies in ANTICOVID trial, and the 5 main randomized clinical trials studying**  
 128 **dose escalation anticoagulation in COVID-19 patients**

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Trials	Prophylactic anticoagulation		Weight-based intermediate anticoagulation	Curative anticoagulation
	Lower	Higher		
ANTICOVID, 3 arms	X	X		X
INSPIRATION, 2 bras	X	X <sup>b</sup>	X <sup>a</sup>	
COVIDOSE, 2 arms	X (lower in CW / higher in ICU)		X <sup>b</sup>	
REMAPCAP, 2 arms	X (according to local practice)			X
ATTACC, 2 arms	X (according to local practice)			X
ACTIV-4, 2 arms	X (according to local practice)			X

130 Abbreviations: CW, conventional ward; ICU, intensive care unit

131 <sup>a</sup> enoxaparin, 1 mg/kg

132 <sup>b</sup> adjustment different from that of INSPIRATION; see Table 2

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134 **Table 2 : Experimental arm in COVIDOSE trial with weight-adjusted intermediate anticoagulation expressed**  
 135 **as a percentage of the curative anticoagulation dose.**

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Weight	Weight-based intermediate anticoagulation *	% of the curative dose
50 kg	5000 UI *2/j	100%
60 kg	5000 UI *2/j	83%
70 kg	6000 UI *2/j	86%
80 kg	6000 UI *2/j	75%
90 kg	6000 UI *2/j	67%
100 kg	7000 UI *2/j	70%

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\*Dose for a glomerular filtration rate > 30 ml/mn

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The aim of the ANTICOVID study is to evaluate the efficacy of three anticoagulation strategies, each of which is used in routine practice: low-dose prophylactic anticoagulation, high-dose prophylactic anticoagulation (a two-fold increase in the low dose prophylactic) and curative anticoagulation.

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In the INSPIRATION randomized clinical trial, authors evaluate the effects of high-dose (based on weight) vs. low-dose prophylactic anticoagulation among patients admitted to the intensive care unit.

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The COVIDOSE study aims at evaluating two strategies: a prophylactic anticoagulation strategy (low-dose prophylactic anticoagulation among patients hospitalized in a conventional ward or high-dose prophylactic anticoagulation among severe patients admitted to the intensive care unit) vs. a particular strategy with weight-based doses close to the curative doses ranging from 67% to 100% of the curative anticoagulation dose (Table 2).

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The REMAPCAP, ACTIV-4, and ATTACC international randomized clinical trials aim to evaluate curative anticoagulation compared to prophylactic anticoagulation, at a dose (lower or higher) left at the discretion of the clinician based on local practice.

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Therefore, in order to explore the lowest effective dose (given the bleeding risk of anticoagulation) and to answer the key question of dose escalation anticoagulation among COVID-19 patients, the ANTICOVID trial is needed. Indeed, our study is the only one to investigate in separate arms, lower and higher prophylactic doses, as compared to curative anticoagulation, all used in routine clinical practice (Table 1).

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Thirdly, the primary endpoint of these 5 trials is different from that of ANTICOVID (hierarchical endpoint including all-cause mortality followed by time to clinical improvement).

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Overall, given the many differences with the main randomized clinical trials studying dose escalation anticoagulation among COVID-19 patients, the ANTICOVID trial will provide complementary and essential answers to improve the standard of care of COVID-19 patients. Indeed, the trial targets a well-selected population (notably at lower risk of bleeding), with a suitable primary objective and experimental design, to provide a robust response (lowest effective dose with respect to the bleeding risk of anticoagulation).

174 2.1.4 About comparator strategies/procedures

175 In a large observational cohort of 2,773 COVID-19 patients, Paranjpe et al. found a lower in-hospital  
176 mortality in ventilated patients receiving TA as compared to those receiving PA (29.1% vs. 62.7%). In a  
177 multivariable proportional hazards model, a longer duration of TA was associated with a reduced risk of  
178 mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89;  $p < 0.001$ )<sup>12</sup>. Similar findings were recently  
179 reported by Jonmarker et al<sup>13</sup>.

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181 **2.2 Hypothesis for the study**

182 Macrovascular and microvascular thrombotic events have been reported in COVID-19 patients, in  
183 observational and autopsic studies, respectively. Some institutions have released guidance statement for  
184 dose escalation anticoagulation involving high dose prophylactic anticoagulation (HD-PA) or therapeutic  
185 anticoagulation (TA).

186 Our hypothesis is dual: i) first, that TA and HD-PA strategies mitigate microthrombosis and each limit the  
187 progression of COVID-19, including respiratory failure and multi-organ dysfunction, with in fine a  
188 decreased mortality and duration of disease, as compared to a low-dose PA; ii) second, that TA  
189 outperforms HD-PA in this setting.

190 **2.3 Description of the population to be studied and justification for the choice of participants**

191 The study focuses on adults with severe confirmed COVID-19 pneumonia admitted to the hospital, and  
192 requiring oxygen therapy. The choice of this population is driven by fact that patients with severe COVID-  
193 19 requiring oxygen are at higher risk of microthrombosis. All autopsic studies in COVID-19 showing  
194 endotheliatis and microvascular thrombosis involved patients with severe pneumonia.

195 **2.4 Interventions and products which will be performed or used as standard**

196 Participants randomized to the LD-PA, HD-PA and TA strategies will receive the low weight molecular  
197 heparin (LMWH) tinzaparin, considering its contraindications, recommended dose ranges and monitoring  
198 if applicable, as follows: LD-PA : 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h.

199 If tinzaparin is not punctually available, the use of enoxaparin will be allowed as follows: LD-PA: 4000  
200 IU/24h; HD-PA: 4000 IU/12h; TA: 100 IU/kg/12h.

201 The choice of tinzaparin as first line LMWH is driven by the following arguments: i) it is used in all  
202 participating centers in routine care; ii) the single daily dose facilitates its use in the clinical practice.

203 In the case of renal failure (creatinine clearance  $< 30$  mL/min) occurring after randomization or in case of  
204 invasive procedure at high risk of bleeding, LMWH may be replaced by a continuous intravenous infusion  
205 of unfractionated heparin as follows : LD-PA: 100 IU/kg/24h; HD-PA: 200 IU/kg/24h; TA: 500 IU/kg/24h,  
206 adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per the recommendations.

207 After day-14, or hospital discharge, or in case of an indication for TA, or of serious adverse event related  
208 to anticoagulation, the investigational anticoagulation strategy will be discontinued and anticoagulation  
209 treatment will be left at the discretion of attending physicians.

210

211 In all groups, recommendations for the management of COVID-19 pneumonia will be followed, including  
212 the use of dexamethasone. These recommendations will be subject to modifications based on the new  
213 literature data.

214 **2.5 Interventions added for the research**

215

216 The three studied strategies tested are currently employed in COVID-19 patients as part of routine care. A  
217 phone call will be performed at Day-28 and Day-90, unless the patient is still hospitalized. No invasive act  
218 will be added by the research.

219 **2.6 Summary of the known and foreseeable benefits and risks for the research participants**

220

221 The anticipated benefits include the mitigation by HD-PA and TA of microthrombosis to reduce lung and  
222 organ failure in patients with severe COVID-19 pneumonia, and in fine overall mortality. The anticipated  
223 risks include possible bleeding with TA and heparin induced thrombocytopenia with all strategies.

224 The risks to participants will be minimized by several elements of the study design. The three strategies  
225 tested are currently used in COVID-19 patients with severe pneumonia<sup>5-8</sup>. The exclusion criteria prevent  
226 participation of patients who might be at increased risk of adverse effects of anticoagulation. Patients  
227 participating in this trial will be closely monitored and they will have either the same or more intense  
228 monitoring compared to routine treatment, depending on local clinical practice.

229

230 **3 OBJECTIVES OF THE RESEARCH**

231 **3.1 Main objective of the research**

232

233 The main objective is to compare the efficacy of three anticoagulation strategies (LD-PA, HD-PA, and TA)  
234 to reduce the mortality and the time to clinical improvement in patients with severe COVID-19 pneumonia.

235 **3.2 Secondary objectives**

236

237 The secondary objectives are to compare the benefit and risks of the three strategies (LD-PA, HD-PA, and  
238 TA) regarding:

- 239 - Morbi-mortality and organ function;
- 240 - Thrombotic events;
- 241 - Tolerance of anticoagulation.

242

243 **3.3 Objectives of any ancillary study**

244

245 Patients with thrombosis of the large elastic pulmonary vessels (truncular, lobar, segmental or sub-  
246 segmental) on CTPA will not be randomized and will receive TA for 3 months as recommended<sup>20</sup>  
247 **(Figure1)**.

248 The ancillary study will compare the clinical and biological characteristics of patients with a positive  
249 CTPA (non-randomized) to those of patients with a negative CTPA (randomized in the main study). This  
250 comparison will be based on clinical and paraclinical data collected from all included patients. The aim of



251 this ancillary study is to establish a probability score for pulmonary thrombosis during severe COVID-19  
252 pneumonia.

253 The modalities of TA in patients with a positive CTPA will be left at the discretion of the physician in  
254 charge of the patient and will follow actual guidelines <sup>20</sup>.

255

## 256 **4 Description of the research**

257 Currently, the management of anticoagulation in COVID-19 patients involves three strategies in clinical  
258 routine (LD-PA, HD-PA, TA). In the absence of a randomized trial in this context, the ANTICOVID trial  
259 aims to compare the efficacy and tolerance of these three usual strategies.

260

### 261 **4.1 Primary endpoint**

262

263 The primary endpoint is a hierarchical criterion assessed at Day-28, including all-cause mortality, followed  
264 by the time to clinical improvement calculated in such manner that death constitutes a worse outcome than  
265 more days to clinical improvement.

266 The time (number of days) to clinical improvement is defined as the time from randomization to an  
267 improvement of at least two points (from the status at randomization), using an ordinal clinical scale  
268 derived from a WHO recommended instrument (Table 1 <sup>14</sup>). Clinical improvement will be assessed  
269 through a seven-category ordinal scale derived from the WHO scale, as proposed by Coa et al <sup>15</sup>, using the  
270 following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but  
271 unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized,  
272 requiring supplemental oxygen; 5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive  
273 mechanical ventilation, or both; 6. hospitalized, requiring ECMO, invasive mechanical ventilation, or  
274 both; and 7. death. As all included patients will at least require oxygen supplementation, live discharge  
275 from hospital will represent a minimal 2-points decrease in the 7-points scale, thus a clinical improvement.

276 **Table 1:** The WHO ordinal scale <sup>14</sup>

Statut patient	Description	Points
<b>Healed</b>	No clinical infection, negative PCR RT-PCR for COVID-19	0
<b>Not hospitalized</b>	Asymptomatic with a positive RT-PCR for COVID-19	1
	Symptomatic	2
	Symptomatic, in convalescent ward	3
<b>hospitalized in regular ward</b>	No oxygen therapy	4
	Oxygen by mask or nasal prongs	5
<b>Hospitalised in intensive care unit</b>	Requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both	6
	Invasive ventilation, PaO <sub>2</sub> /FIO <sub>2</sub> >= 150	7
	Invasive ventilation PaO <sub>2</sub> /FIO <sub>2</sub> <150 or catecholamine	8
	Requiring ECMO or dialysis	9
<b>Death</b>	Death	10

277

278 The weaning of ventilation and of supplemental oxygen will be protocolized.

281 **4.2.1.1 Efficacy on morbi-mortality and organ function**

- 283 - Individual components of the composite ranked primary endpoint, including time to clinical  
284 improvement and all-cause death at Day-28, including cardiovascular deaths, non-cardiovascular  
285 deaths, and deaths of undetermined cause. Death from cardiovascular cause is defined as any death due  
286 to refractory cardiogenic shock or unrecovered resuscitated cardio-circulatory arrest of confirmed or  
287 suspected cardiogenic origin;
- 288 - All-cause death at Day-90;
- 289 - Score on WHO Ordinal Scale at Day-28 and 7-points ordinal scale;
- 290 - D-dimers and Sepsis-Induced Coagulopathy Score (SCS) (see detailed definition in **Annex 3**) at Day-  
291 7;
- 292 - Number of days alive and free from supplemental oxygen at Day-28;
- 293 - Proportion of patients needing intubation at Day-28;
- 294 - Number of days alive and free from invasive mechanical ventilation at Day-28;
- 295 - Number of days alive and free from vasopressors at Day-28;
- 296 - Length of intensive care unit stay ;
- 297 - Length of hospital stay;
- 298 - Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L) (see detailed  
299 definition in **Annex 4**) ;
- 300

301 **4.2.1.2 Efficacy on thrombotic events**

- 302 - Proportion of patients with at least one thrombotic event (see detailed definition in **Annex 5**) at Day-28  
303 including:
- 304 ○ Ischemic stroke: acute focal cerebral, spinal, or retinal dysfunction associated with infarction on an  
305 imaging study (computed tomography or magnetic resonance imaging); Hemorrhagic conversion  
306 of an ischemic stroke should be classified as ischemic <sup>21</sup>;
  - 307 ○ Non-cerebrovascular arterial thrombotic event: acute vascular occlusion of the extremities or any  
308 non-cerebrovascular organ confirmed by one or more of the following: standard clinical and  
309 laboratory testing, operative findings, or autopsy findings <sup>21</sup>;
  - 310 ○ Deep venous thrombosis (DVT) confirmed by venous duplex compression ultrasonography  
311 including symptomatic lower extremity proximal DVT, upper extremity DVT, asymptomatic  
312 proximal DVT of the lower extremities <sup>22</sup>;
  - 313 ○ Pulmonary embolism defined as truncular, lobar, segmental or sub-segmental pulmonary  
314 thrombosis identified on CTPA;
  - 315 ○ Central venous catheter (CVC)-related DVT defined as an event that prompted duplex ultrasound  
316 of the ipsilateral extremity in which an acute, proximal large vein thrombosis was confirmed in  
317 association with the CVC or confirmed within 5 days of CVC removal.

319 The assessment of thrombotic events will be carried out with an adjudication committee.

321 **4.2.1.3 Tolerance of anticoagulation**

- 322 - Proportion of patients with at least one major bleeding event (MBE) at Day-28. MBE will be assessed  
323 using the International Society on Thrombosis and Haemostasis (ISTH) definition and life-threatening  
324 bleedings will be assessed using the RE-LY definition (see details definition in **Annex 5**);
- 325 ○ The bleeding event is major if it meets at least one of the following criteria according to the ISTH  
326 definitions <sup>23</sup>: symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal,  
327 intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment

328 syndrome), bleeding associated with a reduction in hemoglobin of  $\geq 2$  g/dl (1.24 mmol/l) or leading  
329 to transfusion of  $\geq 2$  units of blood or packed cells ; fatal bleeding.

330 - Proportion of patients with at least one life-threatening bleeding event at Day-28. The bleeding event is  
331 life-threatening if it meets at least one of the following criteria according to the RE-LY definitions <sup>24</sup>:  
332 fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in hemoglobin of  $\geq 50$  g/L,  
333 or bleeding requiring transfusion of  $\geq 4$  units of blood; necessitating surgical, endoscopic, or  
334 endovascular action.

335 - Proportion of patients with at any bleeding event at Day-28 of randomization including major and  
336 minor bleeding events. Minor bleeding events will be defined as all non-major bleeding events.

337 - Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28  
338

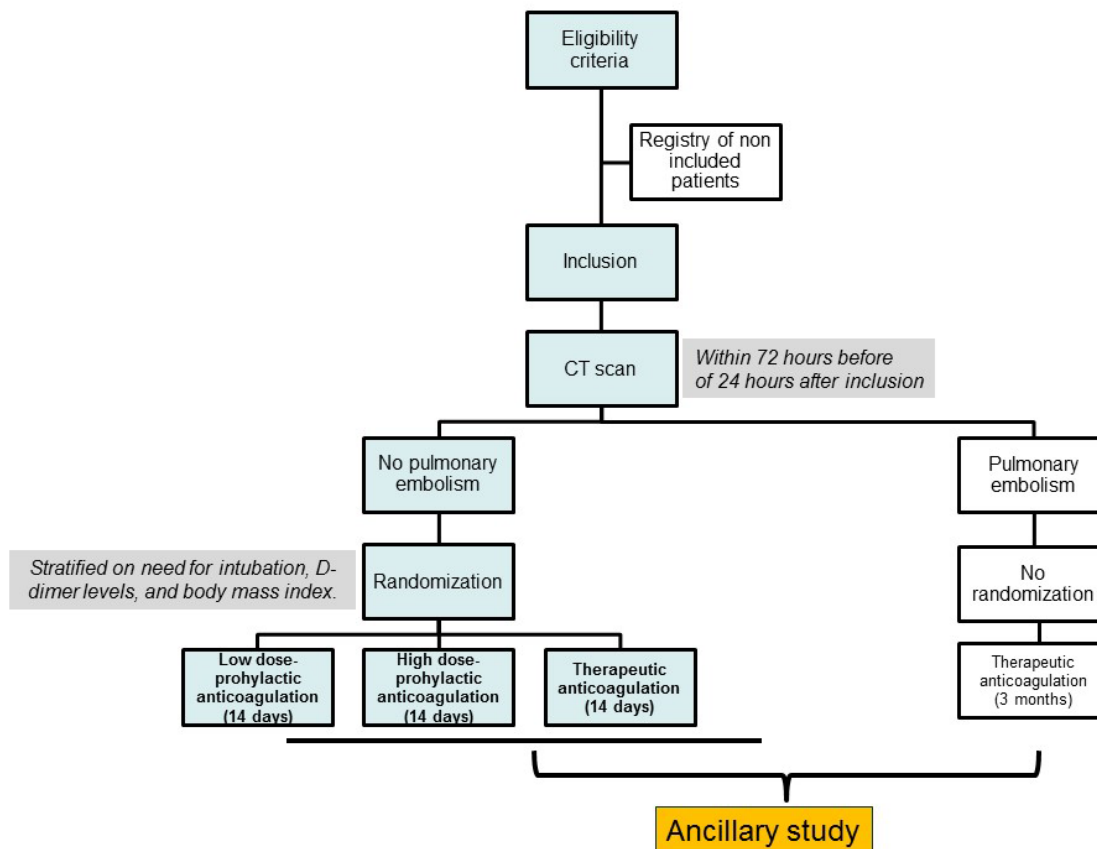
339 The assessment of bleeding events will be carried out with an adjudication committee.  
340

## 341 5 Description of research methodology

### 342 5.1 Design of the study

343

344 The research is a multicenter, parallel group, open-label, randomized controlled superiority trial, aiming at  
345 comparing three usual strategies of anticoagulation. The primary hierarchical criterion assessed at Day-28,  
346 includes all-cause mortality followed by the time to clinical improvement. The three strategies are LD-PA,  
347 HD-PA, and TA, with a 1:1:1 ratio. The experimental schema is displayed in **Figure 1**.



348

349 **Figure 1: Experimental schema.**

350 *Definition of abbreviations: CTPA, computed tomography pulmonary arteries.*

351

## 352 **5.2** Number of participating sites

353

354 This is a multicenter research. Twenty-four university-affiliated hospitals are planned to participate. The  
355 list of centers is the presented in **Annex 6**.

356

## 357 **5.3** Description of measures taken to reduce and prevent biases

### 358 5.3.1 Identification of participants

359

360 The participants in this research will be identified as follows: Site number (3 digits) - Sequential enrolment  
361 number for the site (4 digits) - Surname initial - First name initial. This reference number is unique and  
362 will be used for the entire duration of the study.

### 363 5.3.2 Randomisation

364

365 Randomisation will be carried out within 24 hours after inclusion or CTPA, whichever occurs last. In the  
366 event of a computer breakdown, the 72-hour period between eligibility and inclusion, as well as the 24-  
367 hour period between the inclusion/CTPA and randomization, may exceptionally be extended by a further  
368 24 hours each.

369 A randomization number will be assigned when the participant is randomized. This number will have the  
370 following format: RXXXX. Centralized blocked randomization according to a 1:1:1 ratio will be prepared  
371 by the Clinical Research Unit (URC-MONDOR) before the start of the trial. It will be carried out in  
372 balanced blocks and stratified by hospital center and according to the following criteria at inclusion: need  
373 for intubation (yes or no), D-dimer levels (upper or lower than 3000 ng/ml), and body mass index (upper or  
374 lower than 30 kg/m<sup>2</sup>).

375 The pre-established randomization list will be incorporated in csv format in the Clean Web software, under  
376 the control of the Quality and Risk Management sector of DRCI. The inclusion and randomization of  
377 patients will be carried out directly online by the investigator (secure Internet protocol) using the Clean  
378 Web software, within the framework of the Public Contract concluded between AP-HP and  
379 TELEMEDICINE TECHNOLOGIES S.A., notified on 17/11/2003 and referenced under N° 033845. The  
380 data will be centralized on a server hosted at the Operational Services Department (DSO) of AP-HP, 67  
381 boulevard Bessières, 75017 PARIS.

382 The concentration of D-dimers and the Sepsis Coagulopathy Score (SCS) will be assessed at  
383 randomization. The SCS includes International Normalized ratio, platelet count, and SOFA score.

384

## 385 **6** Implementation of the study

### 386 **6.1** Schedule for the study

387

Duration of enrolment period	6 months
The length of participation for participants, of which:	
Maximum period between screening and enrolment	3 days
Duration of participation	90 days
Total study duration	9 months

388

389 6.1.1 Screening visit

390

391 A systematic daily check of all patients hospitalized with a positive RT-PCR (either upper or lower  
392 respiratory tract) for COVID-19 (SARS-CoV-2) in the participating centers will be performed, looking for  
393 inclusion and non-inclusion criteria. The number of patients who do not meet the inclusion criteria will be  
394 reported prospectively on a paper register by each of the participating centers. A patient identification  
395 number as well as the reason for non-inclusion will be noted (local register of non-inclusion in each of the  
396 centers).

397

398 6.1.2 Inclusion visit

399

400 Inclusion (D0) is performed as soon as possible, within 72 hours of hospital admission (if the WHO ordinal  
401 scale is 5 at time of inclusion) or within 72 hours of intensive care unit admission (if the WHO ordinal  
402 scale is 6 or more at time of inclusion).

403 Before inclusion, the informed consent of the patient/next-of-kin is sought by study investigator. In case of  
404 a patient unable to express his/her will, and a next-of-kin unidentified and/or unreachable, an emergency  
405 procedure is applied (see Section 15.1).

406

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
<ul style="list-style-type: none"> <li>- The subject participating in the trial.</li> <li>- Next-of-kin (trustworthy person, close relative)</li> </ul>	<ul style="list-style-type: none"> <li>- Investigator (from the medicine department)</li> <li>- Investigator's representative (from the medicine department)</li> </ul>	<p><u>Case 1</u>: the patient is informed at the inclusion visit if he/she is able to express his/her will</p> <p><u>Case 2</u>: the next-of-kin is informed at the inclusion visit if the patient is unable to express his/her will; the patient is informed when he has recovered his/her ability to express his will</p> <p><u>Case 3</u>: nobody is informed at the inclusion visit if the patient is unable to express his/her will and the next-of-kin is unidentified and/or unreachable (EMERGENCY PROCEDURE); the next-of-kin is informed as soon as he/she is identified and reachable; the patient is informed when he/she has recovered his ability to express his will</p>	<p><u>Case 1</u>: the patient gives his/her consent at the inclusion visit</p> <p><u>Case 2</u>: the next-of-kin gives his/her consent at the inclusion visit if the patient is unable to express his/her will; the patient gives his/her consent to continue his/her participation to the study when he/she has recovered his ability to express his/her will</p> <p><u>Case 3</u>: nobody gives consent at the inclusion visit if the patient is unable to express his/her will and the next-of-kin is unidentified and/or unreachable (EMERGENCY PROCEDURE); the next-of-kin gives his/her consent as soon as he/she is identified and reachable; the patient gives his/her consent to continue his/her participation to the study</p>

407

408 A multidetector CTPA (chest computed tomography with pulmonary angiogram) will be performed within  
 409 72 hours before or 24 hours after inclusion. The CTPA modalities will be standardized across the different  
 410 centers, according to the following recommendations<sup>25</sup>. The injection will consist of 100 to 120 ml of low  
 411 osmolality non-ionic contrast product with a high iodine concentration (300 to 400 mg/mL iodine  
 412 concentration; example: Iomeron 400<sup>®</sup>, BYC laboratories, Paris, France) using an automatic injector, with  
 413 a flow rate of 3 to 5 ml/sec<sup>25</sup>. Helical acquisition will be done in standard filter, 64 x 0.625 mm, from the  
 414 lung bases to the apex during an inspiratory pause; pitch from 0.9 to 1.2; rotation time from 0.5 to 0.6 s.  
 415 The analysis of the pulmonary arteries up to the sub-segmental level will be performed by the radiologists  
 416 in charge of patients, according to usual practice and standards. A thrombus will be taken into account in  
 417 case of intraluminal defect of the contrast material or in case of total occlusion of the vessel by low density  
 418 material.

419 According to guidelines, CTPA is contraindicated in cases of severe renal failure (creatinine clearance  
 420 <30mL/min, which is a criterion for non-inclusion in the study). In case of moderate renal insufficiency  
 421 (creatinine clearance between 30 and 60 mL/min), or if the patient has at least one of the following risk  
 422 factors (age >65 years, diabetes, myeloma, nephrotoxic drugs, injection of iodinated contrast material  
 423 within 72 hours prior to the CT scanner), intravenous hydration will be performed prior to the CT scan.  
 424 The results of the CTPA will be used as follows:

- 425 - If the CTPA is positive (elastic artery thrombosis), the patient will not be randomized and  
 426 will receive TA according to the recommendations for thromboembolic disease.
- 427 - If the CTPA is negative, the patient will be randomized to receive either LD-PA, HD-PA  
 428 or TA, for 14 days (or until hospital discharge or weaning of supplemental oxygen during  
 429 48 consecutive hours, whichever comes first).

430 If the patient has a negative CPTA but presents with clinical signs suggestive of deep venous thrombosis at  
 431 inclusion, a complete duplex ultrasound (CDUS) of the lower extremities will be performed<sup>26</sup>; If the  
 432 CDUS is positive, the patient will not be randomized and will receive TA according to the  
 433 recommendations for thromboembolic disease; If the CDUS is negative, the patient will be randomized.

434

### 435 6.1.3 Follow-up visits

436

437 The clinical examination is performed daily as usual. Parameters collected in the study are those usually  
 438 collected during the management of patients with severe pneumonia.

#### 439 **6.1.3.1 Day-7 visit**

440 The concentration of D-dimers and the Sepsis Coagulopathy Score (SCS) will be re-assessed at Day-7. The  
 441 SCS includes International Normalized ratio, platelet count, and SOFA score.

442

#### 443 **6.1.3.2 Day-28 (or hospital discharge visit if it occurs first)**

444 At Day-28 or hospital discharge, the parameters of evolution during hospital stay will be collected  
 445 including:

- 446 - the WHO ordinal scale and its components: limitation of activities, oxygen therapy and its modalities  
 447 (nasal prongs, mask, high flow, CPAP, non-invasive ventilation, mechanical ventilation), vasopressor,  
 448 renal replacement therapy, extracorporeal membrane oxygenation, vital status.
- 449 - Thrombotic and hemorrhagic events.

450 - Heparin induced thrombocytopenia.

451

#### 452 6.1.4 Last study visit

453

454 The research does not include any follow-up visit beyond the usual management, except visits at Day-28  
455 and Day-90.

456 If the patient is still in the hospital at Day-28 and Day-90, data will be collected from the patient's medical  
457 records with the possible assistance of a clinical research technician (CRT). Data collected in the medical  
458 record will include length of stay in hospital and intensive care and vital status.

459 If the patient is discharged from the hospital:

460 - the CRT will collect the medical records from the clinical departments where the patient stayed in the  
461 period; these will be analyzed by the investigator who included the patient;

462 - the CRT will collect data on the vital status and occurrence of serious adverse events of the patient:

463 o (if necessary) telephone contact with the patient (3 different attempts, days and times over 15  
464 days);

465 o (if necessary) telephone contact with the physician in charge of the patient during the period;

466 o (if necessary) telephone contact with the patient's treating or referring physician(s);

467 o (if necessary) contact of the town council of the patient birthplace.

468 At Day-90, the patient will be assessed for the EQ-5D 5L questionnaire to provide a simple measure of  
469 his/her health for clinical appraisal.

470

### 471 6.1 Table or diagram summarising the chronology of the study, with distinction between standard 472 care and research

473

<b>Actions</b> (C= care; R= research)	(inclusion)	Day-1 (randomization)		Day-2 to Day-14	Day-15 to Day-28 (or hospital discharge)	+/- 10 days (End of study)
Inclusion and non-inclusion criteria	R					
Informed consent	R					
CT chest X-ray	C					
CTPA		C				
Randomization		R				
Clinical data	C			C	C	
WHO scale score and its components	C	C		C	C	
D-dimers and platelet count		C	C	C		

474	SCS and its components		C	C			
475	Anticoagulation strategy				R		
476	Thrombotic and hemorrhagic events		C		C	C	R
477	Vital status		C		C	C	R
478	Serious adverse event		C		R	R	R
479							

## 480 7 ELIGIBILITY CRITERIA

### 481 7.1 Inclusion criteria

482

- 483 - Age  $\geq$  18 years ;
- 484 - Severe COVID-19 pneumonia, defined by:
- 485     o A newly-appeared pulmonary parenchymal infiltrate; AND
- 486     o a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2);
- 487     AND
- 488     o WHO progression scale  $\geq$  5 (**Table1**).
- 489 - Written informed consent (patient, next of skin or emergency situation).

490

491 In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion

492 for inclusion.

493

### 494 7.2 Exclusion criteria

- 495 - Pregnancy and breast feeding woman;
- 496 - Postpartum (6 weeks);
- 497 - Extreme weights (<40 kg or >100 kg);
- 498 - Patients admitted since more than 72 hours to the hospital (if the WHO ordinal scale is 5 at time of
- 499 inclusion) or since more than 72 hours to the intensive care unit (if the WHO ordinal scale is 6 or more
- 500 at time of inclusion);
- 501 - Need for therapeutic anticoagulation;
- 502 - Bleeding event related to hemostasis disorders, acute clinically significant bleed, current
- 503 gastrointestinal ulcer or any organic lesion with high risk for bleeding
- 504 - Platelet count < 50 G/L;
- 505 - Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;
- 506 - Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or
- 507 neoplasm, acute infectious endocarditis;
- 508 - Severe renal failure (creatinine clearance <30 mL/min);
- 509 - Iodine allergy;
- 510 - Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;
- 511 - History of type II heparin-induced thrombocytopenia;
- 512 - Chronic oxygen supplementation;
- 513 - Moribund patient or death expected from underlying disease during the current admission;
- 514 - Patient deprived of liberty and persons subject to institutional psychiatric care;
- 515 - Patients under guardianship or curatorship;
- 516 - Participation to another interventional research on anticoagulation.

517



	Number of participants
Total number of participants to be included	353 (300 randomized)
Number of centers	24
Enrolment period (months)	6
Number of participants/center	15
<b>Number of participants/center/month</b>	<b>2 to 3</b>

520

521 **8 TERMINATION rules**

522

523 Several situations are possible

524

- 525 - Temporary discontinuation the investigator must document the reason for the arrest and its recovery in  
 526 the source file of the subject and the CRF  
 527 - Premature discontinuation, but the participant remains enrolled in the study until the end of his/her  
 528 participation: the investigator must document the reason  
 529

530 **8.1** Criteria and procedure for premature withdrawal of a participant from the study

531

- 532 - Participants may exit the study at any time and for any reason.
- 
- 533

- 534 - The investigator can temporarily or permanently withdraw a participant from the study for any safety
- 
- 535 reason or if it is in the participant's best interests.

- 536 - If a participant exits the study prematurely, his/her data may be used until the date of the withdrawal of
- 
- 537 his/her consent.

- 538 - If a participant leaves the study prematurely or withdraws consent, any data collected prior to the date
- 
- 539 of premature discontinuation may still be used.
- 
- 540

- 541 - The case report form must list the various reasons why the participant has discontinued the study:

542  Adverse reaction543  Another medical issue544  Personal reasons of the participant545  Explicit withdrawal of consent.  
546

547 In accordance with the usual management of patients with severe COVID-19 pneumonia, the  
548 anticoagulation strategies will be discontinued in the followings cases:

- 549 - Occurrence of major bleeding event according to the ISTH definition (**see annex 5**);
- 550 - Occurrence of an enlarged acute ischemic stroke;
- 551 - Skin necrosis of the injection site;
- 552 - Occurrence of a Type II heparin induced thrombocytopenia;
- 553 - Occurrence of an allergic reaction;
- 554 - Hospital discharge prior to Day-14.

555

556 The TA strategy will be temporarily interrupted if any one of the following conditions is met, prior to the  
557 maximum treatment period (14 days from randomisation); the study drug will be administered again at  
558 least 6 hours after the resolution of the anomaly:

- 559 - Need for therapeutic anticoagulation;
- 560 - Need for lumbar puncture, spinal or epidural anesthesia;
- 561 - Need for surgery.

562

### 563 8.1.1 **Management of a bleeding event**

564 In the occurrence of major or minor bleeding, the origin of bleeding will be investigated and an appropriate  
565 treatment will be initiated. In the occurrence of major bleeding event (MBE), the TA and HD-PA strategies  
566 will be suspended. The following measures will also be performed, as per usual care and  
567 recommendations:

- 568 - An anti-Xa activity assay will be performed immediately;
- 569 - Protamine treatment may be required at the discretion of physician in charge of the patient.

### 570 8.1.2 **Management of heparin-induced thrombocytopenia (HIT)**

571 HIT will be suspected in the presence of a platelet count < 150 Giga/L and/or a relative fall in platelets of  
572 around 30 to 50% compared to the platelet count before any treatment. In the case of HIT suspicion, the  
573 following actions will be taken as per usual care and recommendations:

- 574 - An immediate check of the blood count;
- 575 - The discontinuation of the heparin treatment, if the decrease is confirmed in the absence of another  
576 obvious etiology of thrombocytopenia;
- 577 - In vitro platelet aggregation tests and immunological tests;
- 578 - A specialist hematological opinion will be given to confirm or reject the diagnosis of HIT;
- 579 - If the anticoagulation seems necessary according to the physicians in charge, heparin will be replaced  
580 by another class of antithrombotics as danaparoid sodium or lepirudin in prophylactic or therapeutic  
581 dosage depending on the clinical context.

582

### 583 8.1.3 Full or partial discontinuation of the study

584

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

587

588

## 589 **9 EFFICACY ASSESSMENT**

590 **9.1 Description of efficacy assessment parameters**

591 The efficacy parameters are the primary and secondary efficacy endpoints as defined in **paragraph 4**:

- 592 - All-cause death;
- 593 - Score on WHO Ordinal Scale;
- 594 - D-dimers and Sepsis Coagulopathy Score (SCS);
- 595 - Need for supplemental oxygen;
- 596 - Need for intubation;
- 597 - Need for vasopressors;
- 598 - Length intensive care unit stay and hospital stay;
- 599 - Quality of life and disability;
- 600 - Thrombotic event including ischemic stroke, non-cerebrovascular arterial thrombotic event, deep
- 601 venous thrombosis, pulmonary emboli and central venous catheter-related deep venous thrombosis.
- 602

603 **9.2 Scheduled methods and timetable for measuring, collecting and analysing the efficacy**  
 604 **assessment parameters**

605

606 All efficacy parameters are collected prospectively by the investigator during follow-up visits as defined in  
 607 **section 5.2**. These parameters are routinely collected in the medical record of the patient with severe  
 608 COVID-19 pneumonia. If the patient is discharged before Day-28, vital status will be collected by a  
 609 telephone call from the patient or attending physician or letter to the birth city hall if applicable. All-cause  
 610 death and quality of life and disability will be collected by the investigator at the Day-90 follow up visit (If  
 611 the patient is discharged before Day-90, these parameters will be collected by a telephone call from the  
 612 patient or attending physician or letter to the birth city hall if applicable).

613

614

615

616

<b>Actions</b> (C= care; R= research)	(inclusion) Day-1	(randomization) Day-1		Day-2 to Day-14 Day-1 to Day-20	(or hospital discharge)	+/- 10 days (End of study)
WHO scale score and its components	C	C		C	C	
D-dimers		C	C	C		
SCS and its components		C	C			
Anticoagulation strategy				R		
Thrombotic events		C		C	C	R
Vital status		C		C	C	R
Quality of life questionnaire (EQ5D5L)						R

617

**10 VIGILANCE**

618 The tolerance parameters are the secondary safety endpoints as defined in **section 4.2** and correspond to  
 619 potential adverse events related to the study strategies.

620 During this research, adverse events (serious and otherwise) do not need to be reported to the sponsor. The  
621 report must instead be made as part of the vigilance procedure applicable to the product or intervention  
622 under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device,  
623 etc.). In addition, an independent adjudication committee will review thrombotic and bleeding events as  
624 well as serious adverse events.

## 625 10.1 Definitions

626 According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

### 627 • Adverse event

628 Any untoward medical occurrence in a study participant, which does not necessarily have a causal  
629 relationship with the study or with the product subject to the study.

### 630 • Adverse reaction

631 Adverse event occurring in a person enrolled in a study involving human participants, when this event is  
632 related to the study or to the product being studied.

### 633 • Serious adverse event or reaction

634 Any adverse event or reaction that results in death, threatens the life of the research participant, requires  
635 hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results  
636 in a congenital abnormality or deformity.

### 637 • Unexpected adverse reaction

638 Any adverse reaction for which the nature, severity or progression are not consistent with information  
639 pertaining to the products, acts practiced and methods used during the study.

640

641 Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor  
642 not relating to a health product (ANSM):

### 643 • Emerging safety issue

644 Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product  
645 under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical  
646 trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

647 For example, this concerns:

- 648 • any clinically significant increase in the frequency of an expected serious adverse reaction;
- 649 • early termination or a temporary halt for safety reasons for a trial carried out in another country with  
650 the same product (act or method) as the one being studied in France;
- 651 • suspected unexpected serious adverse reactions in participants who have terminated the trial and of  
652 which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.  
653

## 654 10.2 The role of the investigator

655

656 **For each adverse event, the investigator must assess its severity** and report all serious and non-serious  
657 adverse events in the case report form (e-CRF).

658 The investigator must **document** serious adverse events **as thoroughly as possible** and provide a  
659 definitive medical diagnosis, if possible.

660 The investigator must **assess the intensity** of the adverse events by using general terms:

- 661 ○ *Mild: tolerated by the patient, does not interfere with daily activities*
- 662 ○ *Moderate: sufficiently uncomfortable to affect daily activities*
- 663 ○ *Serious: prevents daily activities.*

664 The investigator must **assess the causal relationship between** a serious adverse events and strategies  
665 investigated by the study.

666 The method used by the investigator is based on the WHO Uppsala Monitoring Centre Method), and uses  
667 the following 4 causality terms:

- 668 • Certain
- 669 • Probable/likely
- 670 • Possible
- 671 • Unlikely (not excluded)

672 Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version  
673 dated 17/04/2012).

674 **Table: WHO-UMC : causality categories**

Causality term	Assessment criteria*
<b>Certain to occur</b>	<ul style="list-style-type: none"><li>· Event or laboratory test abnormality, with plausible time relationship to drug intake**</li><li>· Cannot be explained by disease or other drugs</li><li>· Response to withdrawal plausible (pharmacologically, pathologically)</li><li>· Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)</li><li>· Rechallenge satisfactory, if necessary</li></ul>
<b>Probable/Likely</b>	<ul style="list-style-type: none"><li>· Event or laboratory test abnormality, with reasonable time relationship to drug intake**</li><li>· Unlikely to be attributed to disease or other drugs</li><li>· Response to withdrawal clinically reasonable</li><li>· Rechallenge not required</li></ul>
<b>Possible</b>	<ul style="list-style-type: none"><li>· Event or laboratory test abnormality, with reasonable time relationship to drug intake**</li><li>· Could also be explained by disease or other drugs</li><li>· Information on drug withdrawal may be lacking or unclear</li></ul>
<b>Unlikely</b>	<ul style="list-style-type: none"><li>· Event or laboratory test abnormality, with a time to drug intake**</li><li>· that makes a relationship improbable (but not impossible)</li><li>· Disease or other drugs provide plausible explanations</li></ul>

675 \*All points should be reasonably complied with

676 \*\*Or study procedures

677

678 **10.2.1 Serious adverse events that do not require the investigator to notify the**  
679 **sponsor without delay**

680

681 A serious adverse event is any untoward medical occurrence that:

- |   |
|---|
| <ul style="list-style-type: none"><li>682 1- results in death</li><li>683 2- is life-threatening to the participant enrolled in the study</li><li>684 3- requires hospitalisation or prolongation of existing hospitalisation</li><li>685 4- results in persistent or significant disability/incapacity</li><li>686 5- is a congenital anomaly/birth defect</li></ul> |
|---|

687

688 **10.2.2 Specific features of the protocol**

- 689 • Adverse events deemed “medically significant”

690 - Thrombotic and bleeding events

691

692 Serious adverse events that do not require the investigator to notify the sponsor without delay

693 • These serious adverse events are only recorded in the case report forms; a data retrieval of the  
694 case report forms will be implemented for serious adverse events every 60 patients. The  
695 primary objective of the trial is to assess the efficacy of anticoagulation strategies in reducing  
696 the mortality and the time to clinical improvement in patients with severe COVID-19. Severe  
697 COVID-19 also has a significant mortality rate. Thrombotic and bleeding events are secondary  
698 endpoints.

699

700 • Deaths, and episodes of thrombosis and bleeding, do not need to be notified to the sponsor  
701 without delay but will be recorded in the case report form. A CRF extraction of all deaths, and  
702 episodes of thrombosis and bleeding will be realized every 60 inclusions. Thrombotic and  
703 bleeding events will be adjudicated by an independent Adjudication committee every 60  
704 inclusions.

705

### 706 10.3 Role of the adjudication committee

#### 707 10.3.1 Analysis and declaration of thrombotic and bleeding events, as well as serious 708 adverse events

709 The adjudication committee assesses:

710 - thrombotic and bleeding events

711 - the **seriousness** of all the adverse events reported

712 - the **causal relationship** with each specific strategy tested by the study,

713 All serious adverse events which the investigator and/or the adjudication committee believe could  
714 have a causal relationship with the strategy tested

715 - the **expected or unexpected nature** of the serious adverse reactions

716 Any serious adverse reaction is considered to be unexpected when the nature, severity or  
717 progression are not consistent with information pertaining to the strategies tested.

718

719 **Serious adverse events** likely to be related to the strategies tested :

720 - *major bleeding events*

721 - *life threatening bleeding events*

722 The sponsor must notify all the investigators involved about any information that could adversely affect the  
723 safety of the research participants.

#### 724 10.3.2 Analysis and declaration of other safety data

725 Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new  
726 data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications  
727 in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend  
728 or halt or modify the study protocol or similar studies.

729 The adjudication committee will inform the sponsor without delay upon knowledge of any emerging safety  
730 issues.

731 The sponsor will inform the competent authority and the Research Ethics Committee without delay upon  
732 knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

733 Following the initial declaration of any emerging safety issues, the sponsor will address to competent  
734 authorities any additional relevant information about the emerging safety issue in the form of a follow-up  
735 report, which must be sent no later than 7 days from learning of the information.

## 736 **11 Specific study committees**

### 737 **11.1 Steering committee**

738

739 The trial steering committee (TSC) will oversee the overall conduct of the trial. The TSC will make  
740 recommendations regarding all trial-related decisions.

741 Members:

742 - principal investigator (Dr Vincent LABBE),

743 - scientific supervisor (Pr Armand MEKONTSO DESSAP),

744 - biostatistician (Pr Etienne AUDUREAU),

745 - the sponsor's appointed representatives for the trial: Clinical Research Associate in charge of the project  
746 and project manager URC DRCI (URC des Hôpitaux Universitaires Henri Mondor) and project manager of  
747 the DRCI promotion unit.

748 Role:

749 - Define the overall structure of the study, coordinate information, determine the initial methodology and  
750 oversee the trial.

751 - Propose procedures to be followed during the study, acknowledging any recommendations from the  
752 Steering Committee.

### 753 **11.2 Adjudication committee**

754 An adjudication committee will independently adjudicate the thrombotic and bleeding events during the  
755 trial, as well as the serious adverse events.

756 Members:

757 - Pr Nadia AISSAOUI

758 - Dr Mathieu SCHMIDT

759

760 Role:

761 - Review and adjudicate reported thrombotic and bleeding events, as well as deaths and serious adverse  
762 events

763 - The committee will meet after every 60 inclusions in the study.

764

765

## 766 **12 data management**

767 **12.1** Data collection procedures

768

769 Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in  
770 collaboration with URC-MONDOR.

771

772 **12.2** Identification of data recorded directly in the CRFs which will be considered as source data

773

774 Vital status at Day-28 and Day-90, unless the patient is still hospitalized and EQ5D5L.

775

776 **12.3** Right to access data and source documents

777

778 12.3.1 Data access

779

780 In accordance with GCPs:

781 - the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to  
782 all locations where the study will be carried out, the source data, the source documents and the reports, for  
783 the purposes of the sponsor's quality control and audit procedures.

784 - the investigators will ensure the persons in charge of monitoring, quality control and auditing the research  
785 have access to the documents and personal data strictly necessary for these tasks, in accordance with the  
786 statutory and regulatory provisions in force

787

788 12.3.2 Source documents

789

790 Source documents are defined as any original document or item that can prove the existence or accuracy of  
791 a data or a fact recorded during the study. These documents will be kept by the investigator, or by the  
792 hospital in the case of a hospital medical file, for 15 years.

793

794 12.3.3 Data confidentiality

795

796 The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé*  
797 *Publique* (French Public Health Code) will take all necessary precautions to ensure the confidentiality of  
798 information relating to the study, the study participants and in particular their identity and the results  
799 obtained.

800 These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance  
801 with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).



802 During and after the research involving human participants, all data collected concerning the participants  
803 and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-  
804 identifying.

805 Under no circumstances shall the names and addresses of the participants involved be shown. Only the  
806 participant's initials will be recorded, accompanied by an encoded number specific to the study indicating  
807 the order of enrolment.

808 The sponsor will ensure that each participant has given written permission for any personal information  
809 about him or her which is strictly necessary for the quality control of the study to be accessed.

#### 810 **12.4** Data processing and storage of research documents and data

811

##### 812 12.4.1 Identification of the data processing manager and location(s)

813

814 Data management and statistical analysis will be performed by URC-MONDOR.

815

##### 816 12.4.2 Data entry

817

818 Non-identifying data will be entered electronically via a web browser.

819

#### 820 **12.5** Data ownership

821

822 AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior  
823 permission.

824

### 825 **13** statistical aspects

#### 826 **13.1** Proposed statistical methods, including the timetable for any planned interim analyses

827 All statistical analyses will be conducted after data review and freezing of data base, using Stata v16.1  
828 (StataCorp, College Station, TX, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna,  
829 Austria), within the Henri Mondor Clinical Research Unit (URC) under the supervision of Pr Etienne  
830 Audureau.

831

##### 832 *Descriptive analyses*

833 Descriptive statistical analyses will be conducted overall and regarding the randomized groups in terms of  
834 general characteristics, demographics, history and baseline characteristics, as well as numbers of  
835 prematurely study treatment withdrawals. Quantitative variables will be presented as mean ( $\pm$ standard  
836 deviation) or median (25-75th percentiles) according to the normality of their distribution as assessed by  
837 means of Shapiro-Wilk tests and graphical methods, and qualitative variables will be presented as numbers  
838 (%).

**840 Primary endpoint analysis**

841 The prespecified primary end point will be a ranked composite score that incorporates death and the time  
842 to clinical improvement, calculated in such manner that death constitutes a worse outcome than more days  
843 to clinical improvement. Each patient will be compared with every other patient in the study and assigned a  
844 score (tie: 0, win: +1, loss: -1) for each pairwise comparison based on whom fared better. If one patient  
845 survived and the other did not, scores of +1 and -1 will be assigned, respectively, for that pairwise  
846 comparison. If both patients in the pairwise comparison survived, the assigned score will depend on which  
847 patient had more days to clinical improvement: the patient with fewer days will receive a score of +1,  
848 while the patient with more days will receive a score of -1. If both patients survived and had the same  
849 number of days to clinical improvement, or if both patients died, they both will be assigned a score of 0 for  
850 that pairwise comparison. For each patient, scores for all pairwise comparisons will be summed, resulting  
851 in a cumulative score for each patient. These cumulative scores will be ranked and compared between  
852 treatment groups via a non-parametrical Mann-Whitney test.

853 No interim analysis is planned. The primary efficacy endpoint will be analyzed using the intention to treat  
854 (ITT) population. Supportive analyses in the per protocol (PP) population will be carried out, so as to  
855 document the patients excluded from PP, investigate the impact on ITT analysis and eventually check  
856 whether similar results are obtained for a robust interpretation. All analyses of secondary endpoints will be  
857 conducted on both ITT and PP populations to assess the robustness of the results.

858

**859 Secondary endpoints**

860 Comparisons between randomized groups at given timepoints will be conducted by use of the Chi square  
861 test or the Fisher's exact test, according to expected numbers in crossings, for categorical variables and by  
862 use of t-tests or non-parametrical Mann-Whitney tests (pairwise comparisons), and ANOVA or Kruskal  
863 Wallis tests (global comparisons for >2 groups) for quantitative variables, as appropriate. Pairwise  
864 comparisons within groups (i.e. across timepoints) will be conducted using tests for paired data, i.e.  
865 McNemar tests for qualitative data, and t-tests for paired data or Wilcoxon signed ranks tests for  
866 continuous data, as appropriate.

867 Individual components of the composite primary endpoint will be assessed as secondary endpoints, i.e. all-  
868 cause mortality at 28-day follow-up and number of days until clinical improvement. To do so, methods for  
869 time-to-event endpoints based on follow-up censored data will be conducted, accounting for the competing  
870 risks of hospital discharge (for mortality evaluation) and death (for time to clinical improvement). Kaplan-  
871 Meier survival curves and cumulative incidence curves will be plotted for each treatment group, and Fine-  
872 Gray regression models will be used to calculate subhazard ratios along with their 95% confidence  
873 intervals and corresponding P-values.

874 Analyses of independent determinants of quantitative secondary endpoints will be performed using  
875 multivariate linear regression analyses adjusting for baseline characteristics and, for global longitudinal  
876 analysis using generalized linear regression mixed models, testing interaction between time, group and  
877 prespecified predictors and entering patient level as a random effect to account for the hierarchical  
878 structure of repeated data.

879

880 Tolerance analysis will be carried out according to the period of appearance and randomization group on  
881 the detailed adverse events relating to the treatment, comparing the rates of occurrence and time of  
882 occurrence.

883

## 884 **13.2 Hypotheses for calculating the required number of participants, and the result**

885

886 The required number of participants is **300 patients randomized (353 patients included)**.

887 Using estimates derived from prior studies led in similar study populations<sup>15</sup>, a sample of at least 300  
888 patients (100 per group) was estimated to provide  $\geq 80\%$  power to detect a statistically significant  
889 difference in the primary ranked composite outcome with 2-sided alpha of 0.017 using a Bonferroni  
890 correction for multiple testing considering 3 pairwise comparisons between randomized arms. Sample size  
891 calculations assumed 28-day mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/- 3  
892 days (standard deviation), 14 days and 12 days, with LD-PA, HD-PA, and TA, respectively. We  
893 hypothesize a 15% rate of positive CTPA<sup>16,17</sup>. In order to randomize 300 patients, we aim at including 353  
894 patients.

895

896 In detail, the sample size calculation was carried out by considering pairwise comparisons between the  
897 groups. For each comparison performed, 5000 samples were simulated using R software.

898 For the first component of the hierarchical primary endpoint (i.e. mortality), survival curves were  
899 simulated based on a Weibull distribution using the R package *simsurv*.

900 For the second component of the hierarchical primary endpoint (i.e. days until clinical improvement)  
901 assessed in alive patients, two different approaches were used regarding the distribution of this parameter  
902 to test the robustness of the results depending on retained hypotheses. First, a normal distribution was  
903 hypothesized with means +/-SD of 16 +/-3, 14 +/-3 and 12 +/-3 days in LD-PA, HD-PA and TA,  
904 respectively. Second, incidence curves for clinical improvement were simulated based on a Weibull  
905 distribution using the R package *simsurv*, with survival medians of 16, 14 and 12 days in LD-PA, HD-PA  
906 and TA, respectively.

907 For both approaches, a systematic 5% rate of patients were identified through simulation as alive patients  
908 at D28 but without achieving clinical improvement, consistent with Cao et al 2020<sup>15</sup>. Standard deviation  
909 and mean number of days until clinical improvement, as well as shape and scale parameters for the  
910 Weibull survival curves simulations were determined from Cao et al 2020<sup>15</sup>, considering median  
911 [interquartile range] survival times and Kaplan Meier curves.

912 Within each sample/pairwise comparison, each patient's score was calculated based on comparing each  
913 patient in one group to all patients in the second group (23). These scores were then compared between  
914 groups by a Mann-Whitney / Wilcoxon test in each of the 5000 samples and the p-value of each test  
915 recorded. For each pairwise comparison, the proportion of tests with a p-value <0.017 was calculated,  
916 providing an estimate for the statistical power achieved.

917

918

### 919 **13.3 State whether subjects who exit the study prematurely will be replaced and in what** 920 **proportion.**

921

922 No participants who withdraw from or drop out of the study will be replaced.

923

### 924 **13.4 Anticipated level of statistical significance**

925 The analysis of the composite primary endpoint will rely on a 1.7% bilateral alpha risk, using a Bonferroni  
926 correction for multiple testing considering 3 pairwise comparisons between randomized arms. A bilateral  
927 alpha of 5% will be used for all comparisons relating to secondary endpoints. No other correction for test

928 multiplicity will be applied for the proposed study, to the exception of pairwise post-hoc comparisons  
929 performed after significant global tests involving multicategorical variables.

930

### 931 **13.5 Statistical criteria for termination of the study**

932 Not applicable.

933

### 934 **13.6 Method for taking into account missing, unused or invalid data**

935 All missing or invalid data will be systematically checked and searched for in patients' medical records. In  
936 addition to complete case analyses based on available data, sensitivity analyses will be led considering  
937 missing values for the primary endpoint as strategy failures, regardless of the strategy, or using approaches  
938 based on multiple imputation by chained equations methodology.

939

### 940 **13.7 Management of modifications made to the analysis plan for the initial strategy.**

941 Any modification of the original statistical analysis plan (as described in the study protocol or in the  
942 statistical analysis plan) will be described and justified in a protocol amendment and/or in the clinical study  
943 reports.

944

### 945 **13.8 Selection of populations**

946 Intention to treat (ITT) population will be defined as patients having signed the consent form to enter the  
947 study and having been randomized to one of the assessed arms. ITT population will thus be analyzed  
948 according to their initial randomized group.

949 Per protocol (PP) population will be defined as patients having been randomized and without any major  
950 deviation to the protocol, including: non-respect of all selection criteria, non-respect of the randomized  
951 treatment allocation and/or duration (wrong strategy received, premature discontinuation of treatment –  
952 except for death), missing data for the primary efficacy endpoints, inclusion in another interventional  
953 study, major protocol deviation identified during a blinded data review before data base freezing.

954 In case of consent withdrawal, only data collected before withdrawal will be used.

955

## 956 **14 QUALITY CONTROL AND ASSURANCE**

### 957 **14.1 General organisation**

958

959 The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study.  
960 The sponsor must implement a quality assurance system to best monitor the implementation of the study in  
961 the investigation centres.

962 For this purpose, the sponsor will define a strategy for opening the centers and may, if necessary, set up a  
963 quality control of the data.

#### 964 14.1.1 Strategy for opening the centres

965

966 The strategy for opening the centres will be determined before the research begins.

967

968 14.1.2 Data quality control

969

970

971 For this Minimal Risks and Burden research study, the appropriate quality control level has been  
972 determined based on the impact and the budget of the research. The sponsor, working in liaison with the  
973 coordinating investigator, will determine this level before the research begins.

974 A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good  
975 completion of the study, for collecting, documenting, recording and reporting all handwritten data, in  
976 accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation  
977 Department.

978 The investigator and the members of the investigator's team agree to make themselves available during  
979 regular Quality Control visits carried out by the Clinical Research Associate.

980

981 **14.2 Case report forms**

982

983 The case report forms should only contain the data needed to analyse the study and publish the results. All  
984 other data needed to monitor the participants during and outside of the study are recorded in the medical  
985 file.

986 All information required by the protocol must be entered in the case report forms. The data must be  
987 collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data  
988 must be coded.

989 Every site will have access to the electronic case report forms via a web-based data collection system.  
990 Investigators will be given a document offering guidance on using this tool.

991 When the investigators complete the case report form via the Internet, the CRA can view the data quickly  
992 and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered.  
993 In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this  
994 end, the investigator must validate any changes to the values in the case report form. An audit trail will be  
995 kept of all changes. A justification can be added when applicable, as a comment.

996 A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study.  
997 The original of this document will be archived by the sponsor. The investigator must archive a copy of the  
998 authenticated document that was issued to the sponsor.

999

1000 **14.3 Management of non-compliances**

1001

1002 Any events that occur as a result of non-compliance – by the investigator or any other individual involved  
1003 in running the study – with the protocol, standard operating procedures, good clinical practices or statutory  
1004 and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

1005 These non-compliances will be managed in accordance with the sponsor's procedures.

1006

1007 **14.4 Audit**

1008

1009 The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the  
1010 inspections carried out by the competent authorities. All data, documents and reports may be subject to  
1011 regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

1012 An audit can be carried out at any time by individuals appointed by the sponsor and independent of those  
1013 responsible for the research. The aim of the audit is to ensure the quality of the study, the validity of the  
1014 results and compliance with the legislation and regulations in force.

1015

1016 The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.

1017 The audit may encompass all stages of the study, from the development of the protocol to the publication  
1018 of the results, including the storage of the data used or produced as part of the study.

1019

1020 **14.5 Principal Investigator's commitment to assume responsibility**

1021

1022 Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated  
1023 personal *curriculum vitae*, signed and dated less than one year, with his/her RPPS number (Répertoire  
1024 Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include  
1025 any previous involvement in clinical research and related training.

1026

1027 Each investigator will commit to comply with legislation and to conduct the study in line with regulations,  
1028 in accordance with the Declaration of Helsinki.

1029

1030 The Principal Investigator at each participating site will sign a commitment of responsibility (standard  
1031 DRCI document) which will be sent to the sponsor's representative.

1032 The investigators and their staff will sign a delegation of duties form specifying each person's role and will  
1033 provide their CVs.

1034

1035 **15 ETHICAL AND LEGAL CONSIDERATIONS**

1036 **15.1 Methods for informing research participants and obtaining their consent**

1037

1038 In accordance with Article L.1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no  
1039 research involving human participants with minimal risks and burden can be carried out on a person  
1040 without his/her freely given and informed consent, obtained expressly after the person has been given the  
1041 information specified in Article L.1122-1 of the aforementioned Code.

1042 The necessary reflection period is given to the individual between the time when he or she is informed and  
1043 when he or she signs the consent form.

1044 The person's freely-given written informed consent will be obtained by the principal investigator, a  
1045 physician representing the investigator or a qualified person, before the person is enrolled on the study.

1046 A copy of the information note and consent form, signed and dated by the research participant and by the  
1047 principal investigator, the physician representing the investigator or a qualified person, will be given to the

1048 individual prior to their participation in the study. The principal investigator or the physician representing  
1049 him/her will keep a copy.

1050 At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the  
1051 consent forms. This envelope will be archived by the sponsor.

1052

1053 In addition, the investigator will specify in the person's medical file the person's participation in the  
1054 research, the procedures for obtaining his/her consent or consent from any other person in the cases set  
1055 forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code),  
1056 as well as the methods used for providing information for the purpose of collecting it. The investigator will  
1057 retain one copy of the signed and dated consent form.

1058 Special circumstances: If the person is physically unable to give his or her written consent, consent may be  
1059 witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative.  
1060 These persons must have be fully independent of the investigator and of the sponsor.

1061 Emergency procedure: If the person is unable to express his will and his/her legally acceptable  
1062 representative is unidentified and/or unreachable at time of inclusion, the investigator may proceed to the  
1063 inclusion of the person without any consent. The investigator must supply any document demonstrating  
1064 that he has extensively tried to identify and/or to reach the legally acceptable representative. In this case of  
1065 emergency procedure, his/her legally acceptable representative gives his consent as soon as he is identified  
1066 and reachable; the person gives his consent to continue his participation to the study when he has recovered  
1067 his ability to express his will.

1068

1069 In practice, the consent will be obtained as follows:

1070 1/ If the patient is capable of participating in the consent process, the investigator will obtain a written  
1071 consent from the patient after an appropriate explanation.

1072 2/ If the patient is unable to give their consent, the investigator will obtain a written consent from his/her  
1073 legally acceptable representative (Article L.1122-2 CSP). As soon as the patient will be capable of  
1074 participating in the consent process, he will be given full information about the study and the investigator  
1075 will obtain a continuation consent from the patient.

1076 3/ If the patient is not capable of participating in the consent process, and his/her legally acceptable  
1077 representative is not present at the time of selection criteria fulfillment, the patient will be included in  
1078 emergency situation (article L1122-1-3 of CSP). The patient or, where applicable, the members of the  
1079 family or the person of trust mentioned in Article L. 1111-6 shall be informed as soon as possible and their  
1080 consent shall be sought from them for the possible continuation of such research. They may also object to  
1081 the use of personal data in the context of this research.

1082

1083 The use of an emergency inclusion in last resort is justified by the following arguments : i) severe COVID-  
1084 19 is a life-threatening situation with a high risk of mortality ; ii) in order to improve patient outcome, an  
1085 anticoagulation heart rate control should be initiated as early as possible after septic shock onset.

1086

1087 **15.2** Prohibition from participating in another clinical study or exclusion period after the study, if  
1088 applicable

1089

1090 Whilst participating in this trial, subjects may not take part in any other interventional clinical study on  
1091 anticoagulation of COVID-19 pneumonia.

### 1092 **15.3** Compensation for participants

1093

#### 1094 15.3.1 Reimbursement of expenses **incurred**

1095

1096 Not applicable.

1097

#### 1098 15.3.2 Compensation

1099

1100 There will be no compensation.

1101

### 1102 **15.4** Registration on the national register of study participants to studies involving human participants

1103

1104 Not applicable.

1105

### 1106 **15.5** Legal obligations

1107

1108 Assistance Publique-Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI  
1109 (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article  
1110 L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique-Hôpitaux de  
1111 Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case,  
1112 notification will be sent to the investigator.

1113

### 1114 **15.6** Request for approval from the CPP (Research Ethics Committee)

1115

1116 Prior to starting the study, AP-HP, as sponsor, must obtain approval from the CPP (Research Ethics  
1117 Committee) for its Minimal Risks and Burden research study, within the scope of the committee's authority  
1118 and in accordance with in force legislation and regulatory requirements.

1119

### 1120 **15.7** Informing the ANSM

1121

1122 AP-HP will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol  
1123 to the ANSM for information.



1124

1125 **15.8** Procedures relating to data protection regulations

1126

1127 The computer file used for this research is implemented in accordance with French (amended  
1128 “Informatique et Libertés” law governing data protection) and European (General Data Protection  
1129 Regulation – GDPR) regulations.

1130 This research is not governed by the CNIL “Reference Method” (MR-001) because of the possible  
1131 inclusion due to an emergency situation without collection of consent at the time of inclusion. The sponsor  
1132 must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data  
1133 processing involving the data required to conduct the research.

1134

1135

1136 **15.9** Amendments to the research

1137

1138 Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor  
1139 for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics  
1140 Committee) before the amendment can be implemented.

1141 The information note and the consent form can be revised if necessary, in particular in case of a substantial  
1142 amendment to the study or if adverse reactions occur.

1143

1144 **15.10** Final study report

1145

1146 The final report for the research involving human participants referred to in Article R1123-67 of the *Code*  
1147 *de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the  
1148 investigator. A report summary drafted according to the reference plan of the competent authority must be  
1149 sent to the competent authority within a period of one year following the end of the study, i.e., the end of  
1150 the participation of the last participant in the study

1151

1152 **15.11** Archiving

1153

1154 Specific documents for a research involving human participants with Minimal Risks and Burden are to be  
1155 archived by the investigator and the sponsor for 15 years following the end of the research.

1156 This indexed archiving includes, in particular:

1157 - A sealed envelope for the investigator containing a copy of all the information notes and consent forms  
1158 signed by all individuals at the centre who participated in the study;

1159 - A sealed envelope for the sponsor containing a copy of all the information notes and consent forms  
1160 signed by all individuals at the centre who participated in the study;

- 1161 - Study binders for the investigator and the sponsor, including (non-exhaustive list):  
1162 • the successive versions of the protocol (identified by the version number and its date), and any  
1163 appendices  
1164 • decisions of the CPP (Research Ethics Committee)  
1165 • any correspondence  
1166 • the enrolment list or register  
1167 • the appendices specific to the research  
1168 • final study report  
1169 - Data collection documents  
1170

## 1171 **16 Funding and Insurance**

### 1172 **16.1 Funding sources**

1173

1174 LEO Pharma

1175

### 1176 **16.2 Insurance**

1177

1178 For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own  
1179 public liability, as well as the public liability for all the physicians involved in the study. The sponsor will  
1180 also provide full compensation for any damages caused by the study to the participant enrolled and their  
1181 beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator.  
1182 Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the  
1183 person who initially consented to participate in the study.

1184

1185 Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE  
1186 through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of  
1187 any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la  
1188 Santé Publique (French Public Health Code).

1189

## 1190 **17 Publication rules**

1191

1192 The author(s) of any publication relating to this study must name the sponsor AP-HP (DRCI) and the  
1193 source of funding.

1194

1195 **This study has been registered on the website <http://clinicaltrials.gov/> under number (*add the*  
1196 *registration number when the study is registered*).**

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1299 **19 List of addenda**

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1301

19.1 Annex 1: Prevention and treatment of thrombosis in hospitalized patients with COVID-19 <sup>7</sup>

	No oxygen therapy	Oxygen therapy	High flow nasal oxygen therapy or mechanical ventilation	Monitoring of anticoagulant treatment
BMI <30 kg/m <sup>2</sup>	<b>LMWH with standard prophylactic dose or fondaparinux</b> (e.g. enoxaparin 4000 IU/24h SC; or 2000 IU/24h SC if Clcr between 15 and 30 ml/min; tinzaparin 3500 IU/24h SC if Clcr >20 ml/min; dalteparin 5000 IU/24h SC si si Clcr >30 ml/min fondaparinux 2.5 mg/24h if Clcr >50 ml/min)			<b>Monitoring of anti-Xa activity:</b> - LMWH: avoid overdose (maintain anti-Xa < 1.2 IU/ml for enoxaparin) - UFH: target 0.3-0.5 IU/ml (+ platelet count every 48 hours)
BMI ≥30 kg/m <sup>2</sup> Without other thrombotic risk factor*	enoxaparin 4000 IU/12h SC enoxaparin 6000 IU/12h SC if weight >120 kg UFH: 200 IU/kg/24h, if Clcr < 30 ml/min.			
BMI ≥30 kg/m <sup>2</sup> with thrombotic risk factor*				
Iterative catheter or renal filter thrombosis Severe Inflammatory Syndrome (e.g. fibrinogen >8 g/L) Hypercoagulability (e.g. D-dimers >3.0 µg/ml) ECMO	LMWH at curative dose e.g. enoxaparin 100 IU/kg/12h SC (actual weight), without exceeding 10,000 IU/12h. UFH 500 IU/kg/24h if Clcr <30 ml/min Re-evaluate the dose in case of multiorgan failure or consumption coagulopathy.			<b>Monitoring of anti-Xa activity:</b> - LMWH: avoid overdose (maintain anti-Xa < 1.2 IU/ml for enoxaparin) - UFH: target 0.5-0.7 IU/ml (+ platelet count every 48 hours)
Long-term anticoagulant treatment				

Intermediate risk    High risk    Very high risk

\*ThromboEmbolic Risk Factors : active cancer, recent personal history of thrombosis...  
 Clcr : Creatinine clearance; LMWH: low molecular weight heparin; UFH: unfractionated heparin

NB: Low risk is not covered.

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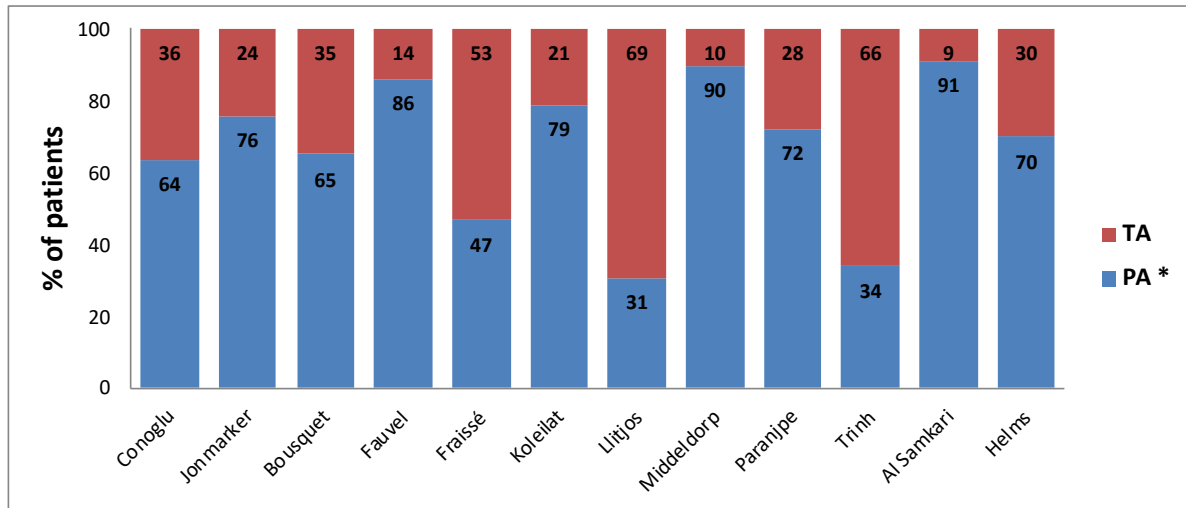
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**19.2** Annex 2: main observational studies reporting the strategies of anticoagulation used in usual practice in hospitalized patients with COVID-19 usual practice about strategy of anticoagulation



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1312 Abbreviations: TA, therapeutic anticoagulation ; PA, preventive anticoagulation

1313 \*including « low dose » and « high dose » preventive anticoagulation

1314 Reference: <sup>4,12,13,27-33</sup>

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1318 **19.3** Annex 3: sepsis-induced Coagulopathy Score <sup>34</sup>

1319

Variable		Points	1320
INR	≤1.2	0	1321
	>1.2 to 1.4	1	1322
	>1.4	2	1323
Platelet count, cells x 10 <sup>9</sup> /L	≥150	0	1324
	100 to <150	1	1325
	<100	2	1326
Total SOFA score*	0	0	1327
	1	1	1328
	≥2	2	1329

1330

1331 \*Summation of the SOFA score's respiratory, cardiovascular, hepatic, and renal SOFA components.

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1335 **19.4** : Annex 4: Quality of life questionnaire (EQ5D5L)

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Variable	Response (Please select the one sentence that best describes your health today ?)
<b>MOBILITY</b>	I have no problems in walking about I have slight problems in walking about I have moderate problems in walking about  I have severe problems in walking about I am unable to walk about
<b>SELF-CARE</b>	I have no problems washing or dressing myself I have slight problems washing or dressing myself I have moderate problems washing or dressing myself  I have severe problems washing or dressing myself I am unable to wash or dress myself
<b>USUAL ACTIVITIES</b> (e.g. work, study, housework, family or leisure activities)	I have no problems doing my usual activities  I have slight problems doing my usual activities I have moderate problems doing my usual activities  I have severe problems doing my usual activities I am unable to do my usual activities
<b>PAIN / DISCOMFORT</b>	I have no pain or discomfort I have slight pain or discomfort I have moderate pain or discomfort  I have severe pain or discomfort I have extreme pain or discomfort
<b>ANXIETY / DEPRESSION</b>	I am not anxious or depressed I am slightly anxious or depressed I am moderately anxious or depressed  I am severely anxious or depressed I am extremely anxious or depressed
<b>HEALTH TODAY</b>	We would like to know how good or bad your health is TODAY. The scale is numbered from 0 to 100 : 100 means the best health you can imagine ; 0 means the worst health you can imagine. Please tell me the number to indicate how your health is TODAY.

1337

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Variable	Définition
<b>Thrombotic event</b>	
Ischemic stroke <sup>21</sup>	Acute focal cerebral, spinal, or retinal dysfunction associated with infarction on an imaging study (CT scan or MRI). Hemorrhagic conversion of an ischemic stroke should be classified as ischemic
Non-cerebrovascular arterial thrombotic event	Acute vascular occlusion of the extremities or any non-cerebrovascular organ by one or more of the following: standard clinical and laboratory testing, operative findings, or autopsy findings <sup>21</sup>
Deep venous thrombosis (DVT)	Confirmed by venous duplex compression ultrasonography or CT-scan <sup>22</sup>
Pulmonary emboli	Venous thromboembolism in pulmonary arteries identified on CT scan
Central venous catheter (CVC)-related DVT	DVT confirmed by venous duplex compression ultrasonography or CT-scan in association with the CVC or confirmed within 5 days of CVC removal
<b>Bleeding event</b>	
Major bleeding event (ISTH definition, <sup>23</sup> )	Meets $\geq 1$ of the following criteria: <ul style="list-style-type: none"> <li>- symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome;</li> <li>- bleeding associated with a reduction in hemoglobin of <math>\geq 2</math> g/dl (1.24 mmol/l) or leading to transfusion of <math>\geq 2</math> U blood or packed cells ;</li> <li>- fatal bleeding.</li> </ul>
Life-threatening bleeding event (RE-LY definition <sup>24</sup> )	Meets $\geq 1$ of the following criteria: <ul style="list-style-type: none"> <li>- fatal bleeding;</li> <li>- symptomatic intracranial bleeding;</li> <li>- bleeding with a decrease in hemoglobin of <math>\geq 50</math> g/L, or bleeding requiring transfusion of <math>\geq 4</math> units of blood; necessitating surgical, endoscopic, or endovascular action;</li> </ul>
Intracranial bleeding (ISTH Definition, <sup>23</sup> )	Intracerebral bleedings, subdural bleedings, epidural bleedings or subarachnoid bleedings.
Fatal bleeding (ISTH Definition, <sup>23</sup> )	Bleeding event that is the primary cause of death or contributes directly to death.

1341 Abbreviations: ISTH, International Society on Thrombosis and Haemostasis; RE-LY, Randomized Evaluation of Long-Term  
 1342 Anticoagulation Therapy.

1343

1344 **19.6 Annex 6 : List of Investigators**

1345

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1350

1351 **3 Final version of Protocol**

1352

1353 Research code number: APHP201624

1354

1355 Title: “ANTIcoagulation in severe COVID-19 patients: a multicenter, parallel-group, open-label,  
1356 randomized controlled trial”

1357 ANTICOVID

1358

1359 Version no. 4.0

1360 dated: 18 / 03 / 2022

1361

1362 The study will be carried out in accordance with the protocol, with current good practices and with  
1363 statutory and regulatory requirements.

1364

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**1 SUMMARY**

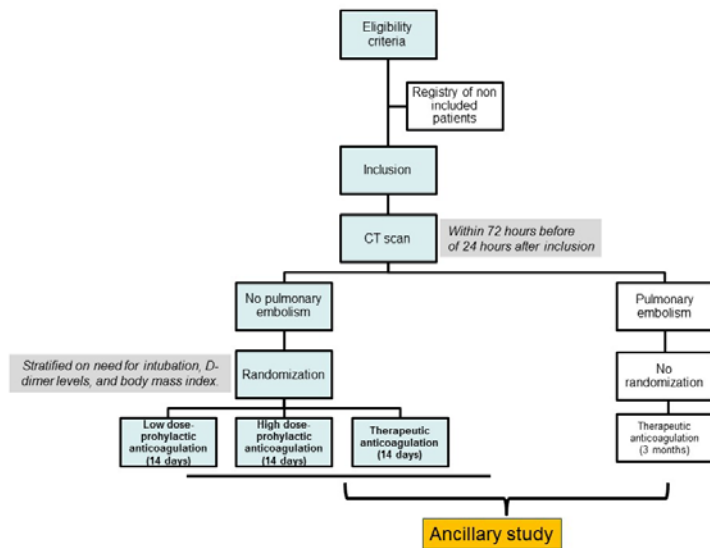
Full title	ANTIcoagulation in severe COVID-19 patients: a multicenter, parallel-group, open-label, randomized controlled trial
Acronym/reference	ANTICOVID
Coordinating investigator	Dr Vincent LABBE
Scientific Director	Pr Armand MEKONTSO-DESSAP
Sponsor	AP-HP
Scientific justification	<p>Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease<sup>1</sup> due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality<sup>2-4</sup>.</p> <p>The incidence of macrovascular thrombotic events varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of arterial or vein thrombosis captured and severity of illness<sup>2-4</sup>. In a cohort of 144 critically ill patients, Al-Samkari et al. reported a 18% (95% CI, 12.1-25.3) rate of overall macrovascular thrombotic events<sup>4</sup>. Based on these observational results in patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several institutions have recently released guidance statement to prevent macrovascular thrombotic events with dose escalation anticoagulation<sup>5,6</sup>. In these recommendations, high-dose prophylactic anticoagulation (HD-PA) and therapeutic anticoagulation (TA) can be employed either empirically or based on the body mass index and increased D-dimer values<sup>5-7</sup>. No randomized trial has validated this approach, and other recent recommendations challenge this approach<sup>6,8</sup>.</p> <p>Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even in the absence of obvious macrovascular thrombotic events. A large review of autopsy findings in COVID-19-related deaths reported micro thrombi in small pulmonary vessels<sup>9</sup>. More generally, COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs lead to widespread microvascular thrombosis with microangiopathy and occlusion of capillaries<sup>2,10,11</sup>. Thus, in severe COVID-19 patients requiring oxygen therapy without initial macrovascular thrombotic event, a HD-PA or a TA could be beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and multi-organ microcirculatory dysfunction. In a large observational cohort of 2,773 COVID-19 patients, Paranjpe et al. found a lower in-hospital mortality</p>

	<p>in ventilated patients receiving TA as compared to those receiving PA (29.1% vs. 62.7%). In a multivariable proportional hazards model, a longer duration of TA was associated with a reduced risk of mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89; p&lt;0.001) <sup>12</sup>. Similar findings were recently reported by Jonmarker et al <sup>13</sup>.</p> <p>To date, no randomized clinical trial has evaluated the best anticoagulation strategy in COVID-19 patients, especially those in whom pulmonary embolism has been excluded on the chest computed tomography with pulmonary angiogram (CTPA). It seems important to rationalize and compare anticoagulation strategies in this context. Our hypothesis is dual: i) first, that TA and HD-PA strategies mitigate microthrombosis and each limit the progression of COVID-19, including respiratory failure and multi-organ dysfunction, with in fine a decreased mortality and duration of disease, as compared to a low-dose PA; ii) second, that TA outperforms HD-PA in this setting.</p>
<p>Main objective and primary endpoint</p>	<p>The main objective is to compare the efficacy of three <u>strategies</u> (LD- PA, HD-PA, and TA) to reduce the mortality and the time to clinical improvement in patients with COVID-19 pneumonia and free from pulmonary embolism at inclusion. Patients with pulmonary embolism at inclusion will not be randomized; they will receive TA as recommended and will be followed up (see ancillary study).</p> <p>The primary endpoint is a hierarchical criterion assessed at 28 days, including all-cause mortality, followed by the time to clinical improvement according to the Finkelstein–Schoenfeld method.</p> <p>This method is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. The pairwise comparison proceeds in hierarchical fashion, using all-cause mortality, followed by the time to clinical improvement when patients cannot be differentiated on the basis of mortality. This method gives a higher importance to all-cause mortality.</p> <p>The time (number of days) to clinical improvement is defined as the time from randomization to an improvement of at least two points (from the status at randomization), using a seven-category ordinal scale derived a WHO recommended instrument <sup>14</sup>, as proposed by Coa et al <sup>15</sup>, using the following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized, requiring supplemental oxygen; 5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6. hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 7. death.</p> <p>The weaning of ventilation and of supplemental oxygen will be protocolized.</p>
<p>Secondary objectives</p>	<p>The secondary objectives are to compare the benefit and risks of the three</p>

and endpoints	<p>strategies (LD-PA, HD-PA, and TA) regarding:</p> <ol style="list-style-type: none"> <li>4. Mortality, morbidity and organ dysfunction; <ul style="list-style-type: none"> <li>- Score on WHO Ordinal Scale and seven category ordinal scale at Day-28;</li> <li>- Number of days alive and free from supplemental oxygen at Day-28;</li> <li>- Proportion of patients needing intubation at Day-28;</li> <li>- Number of days alive and free from invasive mechanical ventilation at Day-28;</li> <li>- Number of days alive and free from vasopressors at Day-28;</li> <li>- Length of intensive care unit stay;</li> <li>- Length of hospital stay;</li> <li>- Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L);</li> <li>- All-cause deaths at Day-28 and Day-90.</li> </ul> </li> <li>5. Efficacy on thrombotic events <ul style="list-style-type: none"> <li>- Proportion of patients with at least one macrothrombotic event including ischemic stroke, non-cerebrovascular arterial thrombotic event, deep venous thrombosis, pulmonary embolism, or central venous catheter-related deep venous thrombosis;</li> <li>- D-dimers and Sepsis-Induced Coagulopathy Score (SCS) at Day-7.</li> </ul> </li> <li>6. Tolerance of anticoagulation <ul style="list-style-type: none"> <li>- Proportion of patients with at least one major bleeding event (MBE) at Day-28;</li> <li>- Proportion of patients with at least one life-threatening bleeding event at Day-28;</li> <li>- Proportion of patients with any bleeding event at Day-28</li> <li>- Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28.</li> </ul> </li> <li>7. Net clinical benefit of anticoagulation as assessed by the absence of all-cause death, thrombotic event, MBE, and HIT at Day-28.</li> </ol> <p>An ancillary study will assess clinical and biological characteristics of severe COVID-19 pneumonia with or without pulmonary embolism to establish a scoring system for COVID-19 related pulmonary embolism diagnosis.</p>
Design of the study	Multicenter open-label randomized controlled superiority trial aiming to compare LD-PA, HD-PA, and TA strategies, with a 1:1:1 ratio.
Population of study participants	Adult patients with oxygen dependent COVID-19 pneumonia.
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Age <math>\geq</math> 18 years;</li> <li>2. Severe COVID-19 pneumonia, defined by: i) a newly-appeared pulmonary parenchymal infiltrate; and ii) a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2); and iii) WHO ordinal scale <math>\geq</math> 5;</li> </ol>



	<p>3. Written informed consent (patient, next of kin or emergency situation).</p> <p>In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion for inclusion.</p>
Exclusion criteria	<p>19. Pregnancy and breast feeding woman;</p> <p>20. Postpartum (6 weeks);</p> <p>21. Extreme weights (&lt;40 kg or &gt;100 kg);</p> <p>22. Patients admitted since more than 72 hours to the hospital (if the WHO ordinal scale is 5 at time of inclusion) or since more than 72 hours to the intensive care unit (if the WHO ordinal scale is 6 or more at time of inclusion);</p> <p>23. Need for therapeutic anticoagulation (except for COVID-related pulmonary thrombosis);</p> <p>24. Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding</p> <p>25. Platelet count &lt; 50 G/L;</p> <p>26. Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;</p> <p>27. Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;</p> <p>28. Severe renal failure (creatinine clearance &lt;30 mL/min);</p> <p>29. Iodine allergy;</p> <p>30. Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;</p> <p>31. History of type II heparin-induced thrombocytopenia;</p> <p>32. Chronic oxygen supplementation;</p> <p>33. Moribund patient or death expected from underlying disease during the current admission;</p> <p>34. Patient deprived of liberty and persons subject to institutional psychiatric care;</p> <p>35. Patients under guardianship or curatorship;</p> <p>36. Participation to another interventional research on anticoagulation.</p>
Interventions or product under investigation	<p>All consecutive adult patients with oxygen dependent COVID-19 pneumonia will be included in the absence of exclusion criteria. A CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion; If a CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis is deemed unchanged by the clinician, the result of that CTPA may be considered at time of inclusion.</p> <ul style="list-style-type: none"> <li>- If the CTPA is positive (pulmonary artery thrombosis), the patient will not be randomized and will receive TA according to the recommendations for thromboembolic disease.</li> <li>- If the CTPA is negative, the patient will be randomized to receive either LD-PA, HD-PA or TA, for 14 days (or until hospital discharge or weaning of supplemental oxygen during 48 consecutive hours, whichever comes first).</li> </ul>



Randomization will be stratified on the following criteria: center, need for intubation (yes or no), D-dimer levels (upper or lower than 3000 ng/ml), and body mass index (upper or lower than 30 kg/m<sup>2</sup>).

Participants randomized to the LD-PA, HD-PA and TA strategies will receive the low weight molecular heparin (LMWH) tinzaparin, considering its contraindications, recommended dose ranges and monitoring if applicable, as follows: LD-PA : 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h. Depending on the type of tinzaparin pre-filled syringe available in the participating center, the dose of 4000 IU/24h will be allowed in place of 3500 IU/24h for LD-PA given their similar indication for this strategy. If tinzaparin is not punctually available, the use of enoxaparin will be allowed as follows: LD-PA: 4000 IU/24h; HD-PA: 4000 IU/12h; TA: 100 IU/kg/12h. The choice of tinzaparin as first line LMWH is driven by the following arguments: i) it is used in routine care; ii) the single daily dose facilitates its use in the clinical practice. In the case of renal failure (creatinine clearance < 30 mL/min) occurring after randomization or in case of invasive procedure at high risk of bleeding, LMWH may be replaced by a continuous intravenous infusion of unfractionated heparin as follows : LD-PA: 100 IU/kg/24h; HD-PA: 200 IU/kg/24h; TA: 500 IU/kg/24h, adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per the recommendations.

After day-14, or hospital discharge, or in case of an indication for TA, or in case of serious adverse event related to anticoagulation, the investigational anticoagulation strategy will be discontinued and anticoagulation treatment will be left at the discretion of attending physicians.

In all groups, recommendations for the management of COVID-19 pneumonia will be followed, including the use of dexamethasone. These

	<p>recommendations will be subject to modifications based on the new literature data.</p> <p>Evaluation criteria will be collected at hospital discharge or at Day-28, and Day-90. The vital status may be obtained by phone call at Day-28 (if the patient has been discharged before Day-28) and at Day-90.</p>
Other interventions added by the study	Interventions added by the study include a phone call at Day-28 and Day-90, unless the patient is still hospitalized. No invasive act will be added by the research.
Expected benefits for the participants and for society	COVID-19 is a critical situation during which the occurrence of macrovascular and microvascular thrombosis is particularly frequent and serious. Anticoagulation is a specific management strategy for thrombosis whose modalities are debated, with major heterogeneities of practices. We propose a randomized trial to rationalize and compare three anticoagulation strategies (LD-PA, HD-PA, and TA) in this context. The results of this trial, in the case our hypothesis is confirmed, will contribute to improve the management of COVID-19 patients with ultimately a potential decrease in the mortality and the time to clinical improvement.
Minimal risks and burden added by the study	No specific risk is added by the study; the three studied strategies are currently employed in COVID-19 patients with pneumonia requiring oxygen therapy as part of routine care.
Scope of the study	Anticoagulation in COVID-19 patients.
Number of participants included	Using estimates derived from the prior observational studies, a sample of at least 300 patients (100 per group) was estimated to provide $\geq 80\%$ power to detect a significant difference in the primary ranked composite outcome with 2-sided alpha of 0.05. Sample size calculations assumed 28-day mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/- 3 days, 14 days and 12 days, with LD-PA, HD-PA, and TA, respectively. We hypothesize a 15% rate of positive CTPA <sup>16,17</sup> . In order to randomize 300 patients, we aim at including 353 patients.
Number of centres	26 recruiting hospitals in France.
Schedule for the study	<ul style="list-style-type: none"> <li>- Inclusion period: 18 months</li> <li>- Participation period (treatment + follow-up): 90 days</li> <li>- Total duration: 21 months</li> </ul>
Number of enrolments expected per site and per month	1
Statistical analysis	No interim analysis is planned. Principal analysis will be performed according to intention to treat principle. The prespecified primary end point will be a ranked composite score that incorporates death and the time to clinical improvement, calculated in such manner that death constitutes a worse outcome than more days to reach clinical improvement.

	<p>Each patient will be compared with every other patient in the study and assigned a score (tie: 0, win: +1, loss: -1) for each pairwise comparison based on whom fared better. If one patient survived and the other did not, scores of +1 and -1 will be assigned, respectively, for that pairwise comparison. If both patients in the pairwise comparison survived, the assigned score will depend on which patient had more days to clinical improvement: the patient with fewer days will receive a score of +1, while the patient with more days will receive a score of -1. If both patients survived and had the same number of days to clinical improvement, or if both patients died, they both will be assigned a score of 0 for that pairwise comparison. For each patient, scores for all pairwise comparisons will be summed, resulting in a cumulative score for each patient. These cumulative scores will be ranked and compared between treatment groups via the Mann-Whitney technique.</p>
Funding sources	Leo Pharma

1369

1371 **2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH**

## 1372 2.1.1 About the condition under investigation

1373 Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory  
1374 syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease<sup>1</sup> due to a state of  
1375 profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and  
1376 increased mortality<sup>2-4</sup>.

1377 The incidence of macrovascular thrombotic event varies from 10 to 30% in COVID-19 hospitalized  
1378 patients depending on the type of arterial or vein thrombosis captured and severity of illness<sup>2-4</sup>. In a cohort  
1379 of 144 critically ill patients, Al-Samkari et al. reported a 18% (95% CI, 12.1-25.3) rate of overall  
1380 macrovascular thrombotic event<sup>4</sup>. Recently, Suh et al. conducted a large review including 27 observational  
1381 studies and 3342 patients with COVID-19. The authors report a pulmonary embolism incidence rate of  
1382 14.8% (95% CI: 8.5, 24.5; I2 = 0.94) despite prophylactic anticoagulation (PA) (24). Based on these  
1383 observational results in patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several  
1384 institutions have recently released guidance statement to prevent macrovascular thrombotic event with  
1385 dose escalation anticoagulation including a high dose-preventive anticoagulation (HD-PA) or a therapeutic  
1386 anticoagulation (TA)<sup>5-7</sup>. No randomized trial has validated this approach, and other recent  
1387 recommendations challenge this approach<sup>6,8</sup>.

1388 Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even  
1389 in the absence of obvious macrovascular thrombotic event. A large review of autopsy findings in COVID-  
1390 19-related death reported micro thrombi in small pulmonary vessels<sup>9</sup>. More generally, COVID-19-induced  
1391 endothelitis and coagulopathy across vascular beds of different organs lead to widespread microvascular  
1392 thrombosis with microangiopathy and occlusion of capillaries<sup>2,10,11</sup>. Thus, in severe COVID-19 patients  
1393 requiring oxygen therapy without initial macrovascular thrombotic event, a HD-PA or a TA could be  
1394 beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and multi-  
1395 organ microcirculatory dysfunction. In a large observational cohort of 2,773 COVID-19 patients, Paranjpe  
1396 et al. found a lower in-hospital mortality in ventilated patients receiving TA as compared to those receiving  
1397 PA (29.1% vs. 62.7%). In a multivariable proportional hazards model, a longer duration of TA was  
1398 associated with a reduced risk of mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89; p<0.001)<sup>12</sup>.  
1399 Similar findings were recently reported by Jonmarker et al<sup>13</sup>.

1400

## 1401 2.1.2 Usual practice about anticoagulation strategies in patients with severe COVID-19

1402

1403 Based on observational studies of thrombotic risk, the « Groupe français d'étude pour l'hémostase et la  
1404 thrombose (GFHT) » and the « Groupe d'intérêt en hémostase péri-opératoire (GIHP) » recommended  
1405 three strategies of anticoagulation with dose escalation (LD-PA, HD-PA, and TA) depending on the  
1406 thrombotic risk level<sup>7</sup> as assessed by: i) the severity of COVID-19; ii) the body mass index; iii) the known  
1407 thrombotic risk factor (e.g., active cancer); iv) a severe inflammatory syndrome (e.g., fibrinogen > 8 g/L)  
1408 or hypercoagulability (e.g., D-dimer > 3000 ng/mL) (**Annex 1**).

1409 While acknowledging that a variety of anticoagulation strategies (LD-PA, HD-PA and TA) are currently  
1410 used in routine practice for severe COVID-19, a group of French and European scientific societies<sup>6 8</sup>  
1411 indicated that the optimal dosing in patients with severe COVID-19 remains unknown and warrants further

1412 prospective investigations. Moreover, they acknowledged the difficulty to evaluate the specific thrombotic  
1413 risk for each patient, even with the use of D-dimers, whose thresholds are not consensual <sup>8</sup>.

1414

1415 Current practices for the management of thrombotic risk in patients with severe COVID-19 are very  
1416 heterogeneous. **Annex 2** presents the main observational studies reporting the strategies of anticoagulation  
1417 used in usual practice in hospitalized patients with COVID-19. Three usual strategies are identified:

1418 - A TA is used in one third of patients;

1419 - A PA is used in two-thirds of patients. The dose (“low” or “high”) of PA is not always reported.

1420 Jonmarker et al. reported in 152 intensive care unit patients the use of LD-PA and HD-PA in 44% and 32%  
1421 of patients, respectively. The TA was administrated in 24% of patients in that study <sup>13</sup>.

1422

### 1423 2.1.3 Current randomized clinical trials

1424

1425 Several trials are studying various doses for anticoagulation strategy in COVID-19 patients <sup>8</sup>.

1426 In the Iranian INSPIRATION trial recently published online in JAMA on March 18, 2021 <sup>18</sup>, Sadeghipour  
1427 et al. compared the efficacy of a standard low dose prophylactic anticoagulation (40 mg once daily  
1428 enoxaparin) with a weight-based high dose prophylactic anticoagulation (1 mg/kg enoxaparin) among  
1429 severe COVID-19 patients admitted to intensive care unit. High dose prophylactic anticoagulation did not  
1430 result in a significant difference in the primary outcome (a composite of adjudicated venous or arterial  
1431 thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days), as  
1432 compared with standard-dose prophylactic anticoagulation. The risk of bleeding was also similar between  
1433 the two groups. In addition, the others main trials (in progress, not published) are the French COVIDOSE  
1434 trial, as well as 3 international trials of similar design from the REMAPCAP, ACTIV-4, and ATTACC  
1435 platforms.

1436 However, **the ANTICOVID study differs** from all these studies for at least three methodological and  
1437 clinical reasons, as detailed below.

1438 Firstly, the inclusion criteria differ because of systematic (ANTICOVID) vs. non-systematic  
1439 (INSPIRATION, COVIDOSE, REMAPCAP, ACTIV-4, ATTACC) investigation of macro-thrombosis,  
1440 which is de facto an indication for curative anticoagulation. ANTICOVID excludes macrothrombosis from  
1441 randomization (chest computed tomography with pulmonary angiogram before randomization to exclude  
1442 pulmonary embolism) and will provide an answer to the specific question of micro thrombosis.  
1443 Microvascular arterial and venous thrombotic events are a major concern in critically ill patients with  
1444 COVID-19, even in the absence of obvious macrovascular thrombotic events. A large review of autopsy  
1445 findings in COVID-19-related death reported micro thrombi in small pulmonary vessels <sup>9</sup>. More generally,  
1446 COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs leads to  
1447 widespread microvascular thrombosis with microangiopathy and occlusion of capillaries <sup>2,10,11</sup>, which may  
1448 ultimately contribute to organ failure. In this respect, the ANTICOVID study is complementary of other  
1449 studies.

1450 On the other hand, in contrast to these 5 other trials, ANTICOVID explicitly excludes patients with a  
1451 higher risk of bleeding (e.g., extreme weight, renal failure with creatinine clearance < 30 ml/min). Indeed,  
1452 renal failure has been shown to be an independent risk factor for bleeding in critically ill patients requiring  
1453 curative anticoagulation <sup>19</sup>. In addition, in patients with acute renal failure after ANTICOVID  
1454 randomization (or in patients undergoing invasive procedures with bleeding risk), low weight molecular

1455 heparin may be replaced by a continuous intravenous infusion of unfractionated heparin, in order to  
 1456 minimize the risk of bleeding. Therefore, ANTICOVID will allow evaluation of anticoagulation dose  
 1457 escalation in a population with a minimized baseline bleeding risk.

1458

1459 Secondly, the anticoagulation strategies studied in the 5 trials are different from ANTICOVID (Table 1).

1460 **Table 1: Anticoagulation strategies in ANTICOVID trial, and the 5 main randomized clinical trials studying**  
 1461 **dose escalation anticoagulation in COVID-19 patients**

1462

Trials	Prophylactic anticoagulation		Weight-based intermediate anticoagulation	Curative anticoagulation
	Lower	Higher		
ANTICOVID, 3 arms	X	X		X
INSPIRATION, 2 bras	X	X <sup>b</sup>	X <sup>a</sup>	
COVIDOSE, 2 arms	X (lower in CW / higher in ICU)		X <sup>b</sup>	
REMAPCAP, 2 arms	X (according to local practice)			X
ATTACC, 2 arms	X (according to local practice)			X
ACTIV-4, 2 arms	X (according to local practice)			X

1463 Abbreviations: CW, conventional ward; ICU, intensive care unit

1464 <sup>a</sup> enoxaparin, 1 mg/kg

1465 <sup>b</sup> adjustment different from that of INSPIRATION; see Table 2

1466

1467 **Table 2 : Experimental arm in COVIDOSE trial with weight-adjusted intermediate anticoagulation expressed**  
 1468 **as a percentage of the curative anticoagulation dose.**

1469

Weight	Weight-based intermediate anticoagulation *	% of the curative dose
50 kg	5000 UI *2/j	100%
60 kg	5000 UI *2/j	83%
70 kg	6000 UI *2/j	86%
80 kg	6000 UI *2/j	75%
90 kg	6000 UI *2/j	67%
100 kg	7000 UI *2/j	70%

1470

1471 \*Dose for a glomerular filtration rate > 30 ml/min

1472 The aim of the ANTICOVID study is to evaluate the efficacy of three anticoagulation strategies, each of  
1473 which is used in routine practice: low-dose prophylactic anticoagulation, high-dose prophylactic  
1474 anticoagulation (a two-fold increase in the low dose prophylactic) and curative anticoagulation.

1475 In the INSPIRATION randomized clinical trial, authors evaluate the effects of high-dose (based on weight)  
1476 vs. low-dose prophylactic anticoagulation among patients admitted to the intensive care unit.

1477 The COVIDOSE study aims at evaluating two strategies: a prophylactic anticoagulation strategy (low-dose  
1478 prophylactic anticoagulation among patients hospitalized in a conventional ward or high-dose prophylactic  
1479 anticoagulation among severe patients admitted to the intensive care unit) vs. a particular strategy with  
1480 weight-based doses close to the curative doses ranging from 67% to 100% of the curative anticoagulation  
1481 dose (Table 2).

1482 The REMAPCAP, ACTIV-4, and ATTACC international randomized clinical trials aim to evaluate  
1483 curative anticoagulation compared to prophylactic anticoagulation, at a dose (lower or higher) left at the  
1484 discretion of the clinician based on local practice.

1485 Therefore, in order to explore the lowest effective dose (given the bleeding risk of anticoagulation) and to  
1486 answer the key question of dose escalation anticoagulation among COVID-19 patients, the ANTICOVID  
1487 trial is needed. Indeed, our study is the only one to investigate in separate arms, lower and higher  
1488 prophylactic doses, as compared to curative anticoagulation, all used in routine clinical practice (Table 1).

1489 Thirdly, the primary endpoint of these 5 trials is different from that of ANTICOVID (hierarchical endpoint  
1490 including all-cause mortality followed by time to clinical improvement).

1491 Overall, given the many differences with the main randomized clinical trials studying dose escalation  
1492 anticoagulation among COVID-19 patients, the ANTICOVID trial will provide complementary and  
1493 essential answers to improve the standard of care of COVID-19 patients. Indeed, the trial targets a well-  
1494 selected population (notably at lower risk of bleeding), with a suitable primary objective and experimental  
1495 design, to provide a robust response (lowest effective dose with respect to the bleeding risk of  
1496 anticoagulation).



1497

1498 2.1.4 About comparator strategies/procedures

1499

1500 In a large observational cohort of 2,773 COVID-19 patients, Paranjpe et al. found a lower in-hospital  
1501 mortality in ventilated patients receiving TA as compared to those receiving PA (29.1% vs. 62.7%). In a  
1502 multivariable proportional hazards model, a longer duration of TA was associated with a reduced risk of  
1503 mortality (adjusted HR: 0.86 per day; 95%CI: 0.82 to 0.89;  $p < 0.001$ )<sup>12</sup>. Similar findings were recently  
1504 reported by Jonmarker et al<sup>13</sup>.

## 1505 **2.2 Hypothesis for the study**

1506

1507 Macrovascular and microvascular thrombotic events have been reported in COVID-19 patients, in  
1508 observational and autopsic studies, respectively. Some institutions have released guidance statement for  
1509 dose escalation anticoagulation involving high dose prophylactic anticoagulation (HD-PA) or therapeutic  
1510 anticoagulation (TA).

1511 Our hypothesis is dual: i) first, that TA and HD-PA strategies mitigate microthrombosis and each limit the  
1512 progression of COVID-19, including respiratory failure and multi-organ dysfunction, with in fine a  
1513 decreased mortality and duration of disease, as compared to a low-dose PA; ii) second, that TA  
1514 outperforms HD-PA in this setting.

1515

## 1516 **2.3 Description of the population to be studied and justification for the choice of participants**

1517

1518 The study focuses on adults with severe confirmed COVID-19 pneumonia admitted to the hospital, and  
1519 requiring oxygen therapy. The choice of this population is driven by fact that patients with severe COVID-  
1520 19 requiring oxygen are at higher risk of microthrombosis. All autopsic studies in COVID-19 showing  
1521 endotheliatis and microvascular thrombosis involved patients with severe pneumonia.

1522

## 1523 **2.4 Interventions and products which will be performed or used as standard**

1524

1525 Participants randomized to the LD-PA, HD-PA and TA strategies will receive the low weight molecular  
1526 heparin (LMWH) tinzaparin, considering its contraindications, recommended dose ranges and monitoring  
1527 if applicable, as follows: LD-PA : 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h.

1528 Depending on the type of tinzaparin pre-filled syringe available in the participating center, the dose of  
1529 4000 IU/24h will be allowed in place of 3500 IU/24h for LD-PA given their similar indication for this  
1530 strategy. If tinzaparin is not punctually available, the use of enoxaparin will be allowed as follows: LD-PA:  
1531 4000 IU/24h; HD-PA: 4000 IU/12h; TA: 100 IU/kg/12h.

1532 The choice of tinzaparin as first line LMWH is driven by the following arguments: i) it is used in all  
1533 participating centers in routine care; ii) the single daily dose facilitates its use in the clinical practice.

1534 In the case of renal failure (creatinine clearance < 30 mL/min) occurring after randomization or in case of  
1535 invasive procedure at high risk of bleeding, LMWH may be replaced by a continuous intravenous infusion  
1536 of unfractionated heparin as follows : LD-PA: 100 IU/kg/24h; HD-PA: 200 IU/kg/24h; TA: 500 IU/kg/24h,  
1537 adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per the recommendations.

1538 After day-14, or hospital discharge, or in case of an indication for TA, or of serious adverse event related  
1539 to anticoagulation, the investigational anticoagulation strategy will be discontinued and anticoagulation  
1540 treatment will be left at the discretion of attending physicians.

1541

1542 In all groups, recommendations for the management of COVID-19 pneumonia will be followed, including  
1543 the use of dexamethasone. These recommendations will be subject to modifications based on the new  
1544 literature data.

## 1545 **2.5 Interventions added for the research**

1546

1547 The three studied strategies tested are currently employed in COVID-19 patients as part of routine care. A  
1548 phone call will be performed at Day-28 and Day-90, unless the patient is still hospitalized. No invasive act  
1549 will be added by the research.

## 1550 **2.6 Summary of the known and foreseeable benefits and risks for the research participants**

1551

1552 The anticipated benefits include the mitigation by HD-PA and TA of microthrombosis to reduce lung and  
1553 organ failure in patients with severe COVID-19 pneumonia, and in fine overall mortality. The anticipated  
1554 risks include possible bleeding with TA and heparin induced thrombocytopenia with all strategies.

1555 The risks to participants will be minimized by several elements of the study design. The three strategies  
1556 tested are currently used in COVID-19 patients with severe pneumonia<sup>5-8</sup>. The exclusion criteria prevent  
1557 participation of patients who might be at increased risk of adverse effects of anticoagulation. Patients  
1558 participating in this trial will be closely monitored and they will have either the same or more intense  
1559 monitoring compared to routine treatment, depending on local clinical practice.

1560

# 1561 **3 OBJECTIVES OF THE RESEARCH**

## 1562 **3.1 Main objective of the research**

1563

1564 The main objective is to compare the efficacy of three anticoagulation strategies (LD-PA, HD-PA, and TA)  
1565 to reduce the mortality and the time to clinical improvement in patients with severe COVID-19 pneumonia.

1566

## 1567 **3.2 Secondary objectives**

1568

1569 The secondary objectives are to compare the benefit and risks of the three strategies (LD-PA, HD-PA, and  
1570 TA) regarding:

1571 - Morbi-mortality and organ function;

- 1572 - Thrombotic events;
- 1573 - Tolerance of anticoagulation.
- 1574 - Net clinical benefit of anticoagulation as assessed by the absence of all-cause death, thrombotic
- 1575 event, major bleeding event and HIT.
- 1576

### 1577 **3.3 Objectives of any ancillary study**

1578

1579 Patients with thrombosis of the large elastic pulmonary vessels (truncular, lobar, segmental or sub-  
1580 segmental) on CTPA will not be randomized and will receive TA for 3 months as recommended<sup>20</sup>  
1581 **(Figure1)**.

1582 The ancillary study will compare the clinical and biological characteristics of patients with a positive  
1583 CTPA (non-randomized) to those of patients with a negative CTPA (randomized in the main study). This  
1584 comparison will be based on clinical and paraclinical data collected from all included patients. The aim of  
1585 this ancillary study is to establish a probability score for pulmonary thrombosis during severe COVID-19  
1586 pneumonia.

1587 The modalities of TA in patients with a positive CTPA will be left at the discretion of the physician in  
1588 charge of the patient and will follow actual guidelines<sup>20</sup>.

1589

## 1590 **4 Description of the research**

1591 Currently, the management of anticoagulation in COVID-19 patients involves three strategies in clinical  
1592 routine (LD-PA, HD-PA, TA). In the absence of a randomized trial in this context, the ANTICOVID trial  
1593 aims to compare the efficacy and tolerance of these three usual strategies.

### 1594 **4.1 Primary endpoint**

1595

1596 The primary endpoint is a hierarchical criterion assessed at Day-28, including all-cause mortality, followed  
1597 by the time to clinical improvement calculated in such manner that death constitutes a worse outcome than  
1598 more days to clinical improvement.

1599 The time (number of days) to clinical improvement is defined as the time from randomization to an  
1600 improvement of at least two points (from the status at randomization), using an ordinal clinical scale  
1601 derived from a WHO recommended instrument (Table 1<sup>14</sup>). Clinical improvement will be assessed  
1602 through a seven-category ordinal scale derived from the WHO scale, as proposed by Coa et al<sup>15</sup>, using the  
1603 following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but  
1604 unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized,  
1605 requiring supplemental oxygen; 5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive  
1606 mechanical ventilation, or both; 6. hospitalized, requiring ECMO, invasive mechanical ventilation, or  
1607 both; and 7. death. As all included patients will at least require oxygen supplementation, live discharge  
1608 from hospital will represent a minimal 2-points decrease in the 7-points scale, thus a clinical improvement.

1609

1610

Statut patient	Description	Points
Healed	No clinical infection, negative PCR RT-PCR for COVID-19	0
Not hospitalized	Asymptomatic with a positive RT-PCR for COVID-19	1
	Symptomatic	2
	Symptomatic, in convalescent ward	3
hospitalized in regular ward	No oxygen therapy	4
	Oxygen by mask or nasal prongs	5
Hospitalised in intensive care unit	Requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both	6
	Invasive ventilation, PaO <sub>2</sub> /FIO <sub>2</sub> ≥ 150	7
	Invasive ventilation PaO <sub>2</sub> /FIO <sub>2</sub> <150 or catecholamine	8
	Requiring ECMO or dialysis	9
Death	Death	10

1611

1612 **Table 1:** The WHO ordinal scale <sup>14</sup>

1613 The weaning of ventilation and of supplemental oxygen will be protocolized.

## 1614 **4.2** Secondary endpoints

1615

### 1616 **4.2.1.1** Efficacy on morbi-mortality and organ function

1617

- 1618 - Individual components of the composite ranked primary endpoint, including time to clinical
- 1619 improvement and all-cause death at Day-28, including cardiovascular deaths, non-cardiovascular
- 1620 deaths, and deaths of undetermined cause. Death from cardiovascular cause is defined as any death due
- 1621 to refractory cardiogenic shock or unrecovered resuscitated cardio-circulatory arrest of confirmed or
- 1622 suspected cardiogenic origin;
- 1623 - All-cause death at Day-90;
- 1624 - Score on WHO Ordinal Scale at Day-28 and 7-points ordinal scale;
- 1625 - D-dimers and Sepsis-Induced Coagulopathy Score (SCS) (see detailed definition in **Annex 3**) at Day-
- 1626 7;
- 1627 - Number of days alive and free from supplemental oxygen at Day-28;
- 1628 - Proportion of patients needing intubation at Day-28;
- 1629 - Number of days alive and free from invasive mechanical ventilation at Day-28;
- 1630 - Number of days alive and free from vasopressors at Day-28;
- 1631 - Length of intensive care unit stay ;
- 1632 - Length of hospital stay;
- 1633 - Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L) (see detailed
- 1634 definition in **Annex 4**) ;
- 1635

### 1636 **4.2.1.2** Efficacy on thrombotic events

- 1637 - Proportion of patients with at least one thrombotic event (see detailed definition in **Annex 5**) at Day-28
- 1638 including:
  - 1639 ○ Ischemic stroke: acute focal cerebral, spinal, or retinal dysfunction associated with infarction on an
  - 1640 imaging study (computed tomography or magnetic resonance imaging); Hemorrhagic conversion
  - 1641 of an ischemic stroke should be classified as ischemic <sup>21</sup>;
  - 1642 ○ Non-cerebrovascular arterial thrombotic event: acute vascular occlusion of the extremities or any
  - 1643 non-cerebrovascular organ confirmed by one or more of the following: standard clinical and
  - 1644 laboratory testing, operative findings, or autopsy findings <sup>21</sup>;

- 1645 ○ Deep venous thrombosis (DVT) confirmed by venous duplex compression ultrasonography  
1646 including symptomatic lower extremity proximal DVT, upper extremity DVT, asymptomatic  
1647 proximal DVT of the lower extremities<sup>22</sup>;  
1648 ○ Pulmonary embolism defined as truncular, lobar, segmental or sub-segmental pulmonary  
1649 thrombosis identified on CTPA;  
1650 ○ Central venous catheter (CVC)-related DVT defined as an event that prompted duplex ultrasound  
1651 of the ipsilateral extremity in which an acute, proximal large vein thrombosis was confirmed in  
1652 association with the CVC or confirmed within 5 days of CVC removal.

1653

1654 The assessment of thrombotic events will be carried out with an adjudication committee.

1655

#### 1656 **4.2.1.3 Tolerance of anticoagulation**

- 1657 - Proportion of patients with at least one major bleeding event (MBE) at Day-28. MBE will be assessed  
1658 using the International Society on Thrombosis and Haemostasis (ISTH) definition and life-threatening  
1659 bleedings will be assessed using the RE-LY definition (see details definition in **Annex 5**);  
1660 ○ The bleeding event is major if it meets at least one of the following criteria according to the ISTH  
1661 definitions<sup>23</sup>: symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal,  
1662 intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment  
1663 syndrome), bleeding associated with a reduction in hemoglobin of  $\geq 2$  g/dl (1.24 mmol/l) or leading  
1664 to transfusion of  $\geq 2$  units of blood or packed cells ; fatal bleeding.  
1665 - Proportion of patients with at least one life-threatening bleeding event at Day-28. The bleeding event is  
1666 life-threatening if it meets at least one of the following criteria according to the RE-LY definitions<sup>24</sup>:  
1667 fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in hemoglobin of  $\geq 50$  g/L,  
1668 or bleeding requiring transfusion of  $\geq 4$  units of blood; necessitating surgical, endoscopic, or  
1669 endovascular action.  
1670 - Proportion of patients with at any bleeding event at Day-28 of randomization including major and  
1671 minor bleeding events. Minor bleeding events will be defined as all non-major bleeding events.  
1672 - Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28

1673

1674 The assessment of bleeding events will be carried out with an adjudication committee.

1675

#### 1676 **4.2.1.4 Net clinical benefit**

- 1677 - Composite of all-cause death, thrombotic event (as defined in paragraph 4.2.1.2), MBE (as defined in  
1678 paragraph 4.2.1.3) at day-28

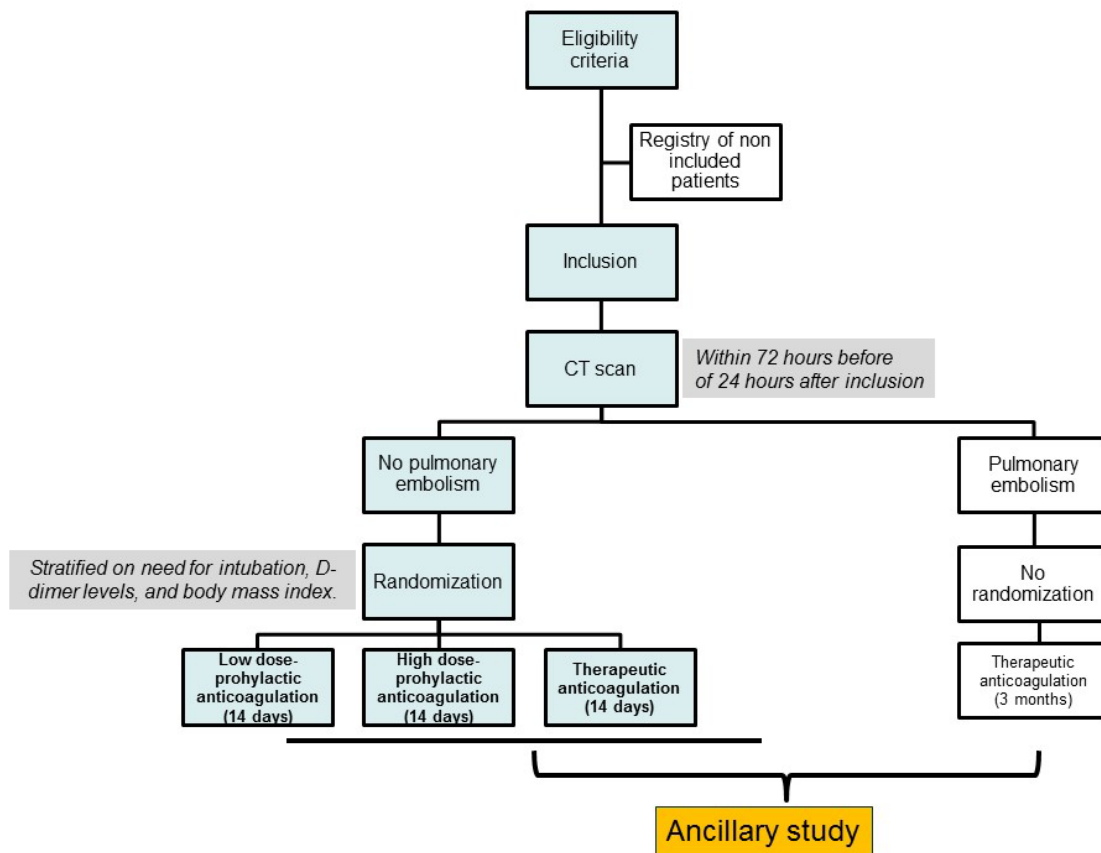
1679

## 1680 **5 Description of research methodology**

### 1681 **5.1 Design of the study**

1682

1683 The research is a multicenter, parallel group, open-label, randomized controlled superiority trial, aiming at  
1684 comparing three usual strategies of anticoagulation. The primary hierarchical criterion assessed at Day-28,  
1685 includes all-cause mortality followed by the time to clinical improvement. The three strategies are LD-PA,  
1686 HD-PA, and TA, with a 1:1:1 ratio. The experimental schema is displayed in **Figure 1**.



1687

1688 **Figure 1: Experimental schema.**

1689 *Definition of abbreviations: CTPA, computed tomography pulmonary arteries.*

1690 **5.2** Number of participating sites

1691

1692 This is a multicenter research. Twenty-six university-affiliated hospitals are planned to participate. The list  
 1693 of centers is the presented in **Annex 6**.

1694

1695 **5.3** Description of measures taken to reduce and prevent biases

1696 5.3.1 Identification of participants

1697

1698 The participants in this research will be identified as follows: Site number (3 digits) - Sequential enrolment  
 1699 number for the site (4 digits) - Surname initial - First name initial. This reference number is unique and  
 1700 will be used for the entire duration of the study.

1701 5.3.2 Randomisation

1702

1703 Randomisation will be carried out within 24 hours after inclusion or CTPA, whichever occurs last. In the  
 1704 event of a computer breakdown, the 72-hour period between eligibility and inclusion, as well as the 24-

1705 hour period between the inclusion/CTPA and randomization, may exceptionally be extended by a further  
1706 24 hours each.

1707 A randomization number will be assigned when the participant is randomized. This number will have the  
1708 following format: RXXXX. Centralized blocked randomization according to a 1:1:1 ratio will be prepared  
1709 by the Clinical Research Unit (URC-MONDOR) before the start of the trial. It will be carried out in  
1710 balanced blocks and stratified by hospital center and according to the following criteria at inclusion: need  
1711 for intubation (yes or no), D-dimer levels (upper or lower than 3000 ng/ml), and body mass index (upper or  
1712 lower than 30 kg/m<sup>2</sup>).

1713 The pre-established randomization list will be incorporated in csv format in the Clean Web software, under  
1714 the control of the Quality and Risk Management sector of DRCI. The inclusion and randomization of  
1715 patients will be carried out directly online by the investigator (secure Internet protocol) using the Clean  
1716 Web software, within the framework of the Public Contract concluded between AP-HP and  
1717 TELEMEDICINE TECHNOLOGIES S.A., notified on 17/11/2003 and referenced under N° 033845. The  
1718 data will be centralized on a server hosted at the Operational Services Department (DSO) of AP-HP, 67  
1719 boulevard Bessières, 75017 PARIS.

1720 The concentration of D-dimers and the Sepsis Coagulopathy Score (SCS) will be assessed at  
1721 randomization. The SCS includes International Normalized ratio, platelet count, and SOFA score.

1722

## 1723 **6 Implementation of the study**

### 1724 **6.1 Schedule for the study**

1725

Duration of enrolment period	18 months
The length of participation for participants, of which:	
Maximum period between screening and enrolment	3 days
Duration of participation	90 days
Total study duration	21 months

1726

#### 1727 *6.1.1 Screening visit*

1728

1729 A systematic daily check of all patients hospitalized with a positive RT-PCR (either upper or lower  
1730 respiratory tract) for COVID-19 (SARS-CoV-2) in the participating centers will be performed, looking for  
1731 inclusion and non-inclusion criteria. The number of patients who do not meet the inclusion criteria will be  
1732 reported prospectively on a paper register by each of the participating centers. A patient identification  
1733 number as well as the reason for non-inclusion will be noted (local register of non-inclusion in each of the  
1734 centers).

1735

#### 1736 *6.1.2 Inclusion visit*

1737

1738 Inclusion (D0) is performed as soon as possible, within 72 hours of hospital admission (if the WHO ordinal  
 1739 scale is 5 at time of inclusion) or within 72 hours of intensive care unit admission (if the WHO ordinal  
 1740 scale is 6 or more at time of inclusion).

1741 Before inclusion, the informed consent of the patient/next-of-kin is sought by study investigator. In case of  
 1742 a patient unable to express his/her will, and a next-of-kin unidentified and/or unreachable, an emergency  
 1743 procedure is applied (see Section 15.1).

1744

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
- The subject participating in the trial. - Next-of-kin (trustworthy person, close relative)	- Investigator (from the medicine department) - Investigator's representative (from the medicine department)	<u>Case 1:</u> the patient is informed at the inclusion visit if he/she is able to express his/her will <u>Case 2:</u> the next-of-kin is informed at the inclusion visit if the patient is unable to express his/her will; the patient is informed when he has recovered his/her ability to express his will <u>Case 3:</u> nobody is informed at the inclusion visit if the patient is unable to express his/her will and the next-of-kin is unidentified and/or unreachable (EMERGENCY PROCEDURE); the next-of-kin is informed as soon as he/she is identified and reachable; the patient is informed when he/she has recovered his ability to express his will	<u>Case 1:</u> the patient gives his/her consent at the inclusion visit <u>Case 2:</u> the next-of-kin gives his/her consent at the inclusion visit if the patient is unable to express his/her will; the patient gives his/her consent to continue his/her participation to the study when he/she has recovered his ability to express his/her will <u>Case 3:</u> nobody gives consent at the inclusion visit if the patient is unable to express his/her will and the next-of-kin is unidentified and/or unreachable (EMERGENCY PROCEDURE); the next-of-kin gives his/her consent as soon as he/she is identified and reachable; the patient gives his/her consent to continue his/her participation to the study when he/she has recovered his/her ability to express his will

1745

1746 A multidetector CTPA (chest computed tomography with pulmonary angiogram) will be performed within  
 1747 72 hours before or 24 hours after inclusion. If a CTPA was performed within 7 days of inclusion and the  
 1748 likelihood of pulmonary artery thrombosis is deemed unchanged by the clinician, the result of that CTPA  
 1749 may be considered at time of inclusion. The CTPA modalities will be standardized across the different  
 1750 centers, according to the following recommendations<sup>25</sup>. The injection will consist of 100 to 120 ml of low  
 1751 osmolality non-ionic contrast product with a high iodine concentration (300 to 400 mg/mL iodine  
 1752 concentration; example: Iomeron 400®, BYC laboratories, Paris, France) using an automatic injector, with  
 1753 a flow rate of 3 to 5 ml/sec<sup>25</sup>. Helical acquisition will be done in standard filter, 64 x 0.625 mm, from the  
 1754 lung bases to the apex during an inspiratory pause; pitch from 0.9 to 1.2; rotation time from 0.5 to 0.6 s.  
 1755 The analysis of the pulmonary arteries up to the sub-segmental level will be performed by the radiologists  
 1756 in charge of patients, according to usual practice and standards. A thrombus will be taken into account in  
 1757 case of intraluminal defect of the contrast material or in case of total occlusion of the vessel by low density  
 1758 material.

1759 According to guidelines, CTPA is contraindicated in cases of severe renal failure (creatinine clearance  
 1760 <30mL/min, which is a criterion for non-inclusion in the study). In case of moderate renal insufficiency  
 1761 (creatinine clearance between 30 and 60 mL/min), or if the patient has at least one of the following risk  
 1762 factors (age >65 years, diabetes, myeloma, nephrotoxic drugs, injection of iodinated contrast material  
 1763 within 72 hours prior to the CT scanner), intravenous hydration will be performed prior to the CT scan.  
 1764 The results of the CTPA will be used as follows:



- 1765 - If the CTPA is positive (elastic artery thrombosis), the patient will not be randomized and will  
1766 receive TA according to the recommendations for thromboembolic disease.  
1767 - If the CTPA is negative, the patient will be randomized to receive either LD-PA, HD-PA or TA,  
1768 for 14 days (or until hospital discharge or weaning of supplemental oxygen during 48 consecutive  
1769 hours, whichever comes first).

1770 If the patient has a negative CPTA but presents with clinical signs suggestive of deep venous thrombosis at  
1771 inclusion, a complete duplex ultrasound (CDUS) of the lower extremities will be performed<sup>26</sup>; If the  
1772 CDUS is positive, the patient will not be randomized and will receive TA according to the  
1773 recommendations for thromboembolic disease; If the CDUS is negative, the patient will be randomized.

1774

### 1775 6.1.3 Follow-up visits

1776

1777 The clinical examination is performed daily as usual. Parameters collected in the study are those usually  
1778 collected during the management of patients with severe pneumonia.

1779

#### 1780 **6.1.3.1 Day-7 visit**

1781 The concentration of D-dimers and the Sepsis Coagulopathy Score (SCS) will be re-assessed at Day-7. The  
1782 SCS includes International Normalized ratio, platelet count, and SOFA score.

1783

#### 1784 **6.1.3.2 Day-28 (or hospital discharge visit if it occurs first)**

1785 At Day-28 or hospital discharge, the parameters of evolution during hospital stay will be collected  
1786 including:

- 1787 - the WHO ordinal scale and its components: limitation of activities, oxygen therapy and its modalities  
1788 (nasal prongs, mask, high flow, CPAP, non-invasive ventilation, mechanical ventilation), vasopressor,  
1789 renal replacement therapy, extracorporeal membrane oxygenation, vital status.  
1790 - Thrombotic and hemorrhagic events.  
1791 - Heparin induced thrombocytopenia.

1792

### 1793 6.1.4 Last study visit

1794

1795 The research does not include any follow-up visit beyond the usual management, except visits at Day-28  
1796 and Day-90.

1797 If the patient is still in the hospital at Day-28 and Day-90, data will be collected from the patient's medical  
1798 records with the possible assistance of a clinical research technician (CRT). Data collected in the medical  
1799 record will include length of stay in hospital and intensive care and vital status.

1800 If the patient is discharged from the hospital:

- 1801 - the CRT will collect the medical records from the clinical departments where the patient stayed in the  
1802 period; these will be analyzed by the investigator who included the patient;  
1803 - the CRT will collect data on the vital status and occurrence of serious adverse events of the patient:  
1804 ○ (if necessary) telephone contact with the patient (3 different attempts, days and times over 15  
1805 days);  
1806 ○ (if necessary) telephone contact with the physician in charge of the patient during the period;

- 1807 ○ (if necessary) telephone contact with the patient's treating or referring physician(s);  
 1808 ○ (if necessary) contact of the town council of the patient birthplace.  
 1809 At Day-90, the patient will be assessed for the EQ-5D 5L questionnaire to provide a simple measure of  
 1810 his/her health for clinical appraisal.

1811

1812 **6.2. Table or diagram summarising the chronology of the study, with distinction between standard care**  
 1813 **and research**

1814

1815

1816

1817

1818

1819

1820

<b>Actions</b> (C= care; R= research)	<b>(inclusion)</b>	<b>(randomization)</b>		<b>Day-2 to Day-14</b>	<b>Day-28 (or hospital stay)</b>	<b>+/- 10 days (End of study)</b>
Inclusion and non-inclusion criteria	R					
Informed consent	R					
CT chest X-ray	C					
CTPA		C*				
Randomization		R				
Clinical data	C			C	C	
WHO scale score and its components	C	C		C	C	
D-dimers and platelet count		C	C	C		
SCS and its components		C	C			
Anticoagulation strategy				R		
Thrombotic and hemorrhagic events		C		C	C	R
Vital status		C		C	C	R
Serious adverse event		C		R	R	R
* A CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion; If a CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis is deemed unchanged by the clinician, the result of that CTPA may be considered at time of inclusion.						

1821

**7 ELIGIBILITY CRITERIA**

1822

**7.1 Inclusion criteria**

1823

- 1824 - Age ≥ 18 years ;

- 1825 - Severe COVID-19 pneumonia, defined by:
- 1826     o A newly-appeared pulmonary parenchymal infiltrate; AND
- 1827     o a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2);
- 1828     AND
- 1829     o WHO progression scale  $\geq 5$  (**Table1**).
- 1830 - Written informed consent (patient, next of skin or emergency situation).
- 1831

1832 In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion

1833 for inclusion.

1834

1835 **7.2 Exclusion criteria**

- 1836 - Pregnancy and breast feeding woman;
- 1837 - Postpartum (6 weeks);
- 1838 - Extreme weights (<40 kg or >100 kg);
- 1839 - Patients admitted since more than 72 hours to the hospital (if the WHO ordinal scale is 5 at time of
- 1840 inclusion) or since more than 72 hours to the intensive care unit (if the WHO ordinal scale is 6 or more
- 1841 at time of inclusion);
- 1842 - Need for therapeutic anticoagulation (except for COVID-related pulmonary thrombosis);
- 1843 - Bleeding event related to hemostasis disorders, acute clinically significant bleed, current
- 1844 gastrointestinal ulcer or any organic lesion with high risk for bleeding
- 1845 - Platelet count < 50 G/L;
- 1846 - Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;
- 1847 - Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or
- 1848 neoplasm, acute infectious endocarditis;
- 1849 - Severe renal failure (creatinine clearance <30 mL/min);
- 1850 - Iodine allergy;
- 1851 - Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;
- 1852 - History of type II heparin-induced thrombocytopenia;
- 1853 - Chronic oxygen supplementation;
- 1854 - Moribund patient or death expected from underlying disease during the current admission;
- 1855 - Patient deprived of liberty and persons subject to institutional psychiatric care;
- 1856 - Patients under guardianship or curatorship;
- 1857 - Participation to another interventional research on anticoagulation.
- 1858

1859 **7.3 Recruitment procedure**

1860

1861 It is a national multicenter study.

1862 Recruitment of patients will be conducted in various departments of selected hospital centers but also in

1863 various “COVID” units that will be created according to the organization of each hospital. Theses

1864 departments and units will be unified in a « COVID center » in each hospital.

1865 In each hospital, declared investigators are likely to recruit and follow patients in that « COVID center ».

	Number of participants
Total number of participants to be included	353 (300 randomized)

Number of centers	26
Enrolment period (months)	18
Number of participants/center	13 to 14
<b>Number of participants/center/month</b>	<b>1</b>

1866

1867

## 8 TERMINATION rules

1868

Several situations are possible

1869

- Temporary discontinuation the investigator must document the reason for the arrest and its recovery in the source file of the subject and the CRF

1870

1871

- Premature discontinuation, but the participant remains enrolled in the study until the end of his/her participation: the investigator must document the reason

1872

1873

1874

### 8.1 Criteria and procedure for premature withdrawal of a participant from the study

1875

1876

- Participants may exit the study at any time and for any reason.

1877

1878

- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.

1879

1880

- If a participant exits the study prematurely, his/her data may be used until the date of the withdrawal of his/her consent.

1881

1882

- If a participant leaves the study prematurely or withdraws consent, any data collected prior to the date of premature discontinuation may still be used.

1883

1884

1885

- The case report form must list the various reasons why the participant has discontinued the study:

1886

Adverse reaction

1887

Another medical issue

1888

Personal reasons of the participant

1889

Explicit withdrawal of consent.

1890

1891

In accordance with the usual management of patients with severe COVID-19 pneumonia, the

1892

anticoagulation strategies will be discontinued in the followings cases:

1893

- Occurrence of major bleeding event according to the ISTH definition (**see annex 5**);

1894

- Occurrence of an enlarged acute ischemic stroke;

1895

- Skin necrosis of the injection site;

1896

- Occurrence of a Type II heparin induced thrombocytopenia;

1897

- Occurrence of an allergic reaction;

1898

- Hospital discharge prior to Day-14.

1899

1900 The TA strategy will be temporarily interrupted if any one of the following conditions is met, prior to the  
1901 maximum treatment period (14 days from randomisation); the study drug will be administered again at  
1902 least 6 hours after the resolution of the anomaly:

- 1903 - Need for therapeutic anticoagulation;
- 1904 - Need for lumbar puncture, spinal or epidural anesthesia;
- 1905 - Need for surgery.

1906

### 1907 8.1.1 Management of a bleeding event

1908 In the occurrence of major or minor bleeding, the origin of bleeding will be investigated and an appropriate  
1909 treatment will be initiated. In the occurrence of major bleeding event (MBE), the TA and HD-PA strategies  
1910 will be suspended. The following measures will also be performed, as per usual care and  
1911 recommendations:

- 1912 - An anti-Xa activity assay will be performed immediately;
- 1913 - Protamine treatment may be required at the discretion of physician in charge of the patient.

### 1914 8.1.2 Management of heparin-induced thrombocytopenia (HIT)

1915 HIT will be suspected in the presence of a platelet count < 150 Giga/L and/or a relative fall in platelets of  
1916 around 30 to 50% compared to the platelet count before any treatment. In the case of HIT suspicion, the  
1917 following actions will be taken as per usual care and recommendations:

- 1918 - An immediate check of the blood count;
- 1919 - The discontinuation of the heparin treatment, if the decrease is confirmed in the absence of another  
1920 obvious etiology of thrombocytopenia;
- 1921 - In vitro platelet aggregation tests and immunological tests;
- 1922 - A specialist hematological opinion will be given to confirm or reject the diagnosis of HIT;
- 1923 - If the anticoagulation seems necessary according to the physicians in charge, heparin will be replaced  
1924 by another class of antithrombotics as danaparoid sodium or lepirudin in prophylactic or therapeutic  
1925 dosage depending on the clinical context.

1926

1927 8.1.3 Full or partial discontinuation of the study

1928

1929 AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the  
1930 inclusion objectives are not met.

1931

## 1932 9 EFFICACY ASSESSMENT

### 1933 9.1 Description of efficacy assessment parameters

1934 The efficacy parameters are the primary and secondary efficacy endpoints as defined in **paragraph 4**:

1935

- 1936 - All-cause death;
- 1937 - Score on WHO Ordinal Scale;
- 1938 - D-dimers and Sepsis Coagulopathy Score (SCS);
- 1939 - Need for supplemental oxygen;

- 1940 - Need for intubation;
- 1941 - Need for vasopressors;
- 1942 - Length intensive care unit stay and hospital stay;
- 1943 - Quality of life and disability;
- 1944 - Thrombotic event including ischemic stroke, non-cerebrovascular arterial thrombotic event, deep
- 1945 venous thrombosis, pulmonary emboli and central venous catheter-related deep venous thrombosis.
- 1946

1947 **9.2** Scheduled methods and timetable for measuring, collecting and analysing the efficacy  
 1948 assessment parameters

1950 All efficacy parameters are collected prospectively by the investigator during follow-up visits as defined in  
 1951 **section 5.2**. These parameters are routinely collected in the medical record of the patient with severe  
 1952 COVID-19 pneumonia. If the patient is discharged before Day-28, vital status will be collected by a  
 1953 telephone call from the patient or attending physician or letter to the birth city hall if applicable. All-cause  
 1954 death and quality of life and disability will be collected by the investigator at the Day-90 follow up visit (If  
 1955 the patient is discharged before Day-90, these parameters will be collected by a telephone call from the  
 1956 patient or attending physician or letter to the birth city hall if applicable).

1957

<b>Actions</b> (C= care; R= research)	(inclusion)	Day-1 (randomization)		Day-2 to Day-14	Day-15 to Day-28 (or hospital discharge)	+/- 10 days (End of study)
WHO scale score and its components	C	C		C	C	
D-dimers		C	C	C		
SCS and its components		C	C			
Anticoagulation strategy				R		
Thrombotic events		C		C	C	R
Vital status		C		C	C	R
Quality of life questionnaire (EQ5D5L)						R

1961 **10 VIGILANCE**

1962 The tolerance parameters are the secondary safety endpoints as defined in **section 4.2** and correspond to  
 1963 potential adverse events related to the study strategies.

1964 During this research, adverse events (serious and otherwise) do not need to be reported to the sponsor. The  
 1965 report must instead be made as part of the vigilance procedure applicable to the product or intervention  
 1966 under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device,  
 1967 etc.). In addition, an independent adjudication committee will review thrombotic and bleeding events as  
 1968 well as serious adverse events.

1969 **10.1 Definitions**

1970 According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

1971 • **Adverse event**

1972 Any untoward medical occurrence in a study participant, which does not necessarily have a causal  
1973 relationship with the study or with the product subject to the study.

1974 • **Adverse reaction**

1975 Adverse event occurring in a person enrolled in a study involving human participants, when this event is  
1976 related to the study or to the product being studied.

1977 • **Serious adverse event or reaction**

1978 Any adverse event or reaction that results in death, threatens the life of the research participant, requires  
1979 hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results  
1980 in a congenital abnormality or deformity.

1981 • **Unexpected adverse reaction**

1982 Any adverse reaction for which the nature, severity or progression are not consistent with information  
1983 pertaining to the products, acts practiced and methods used during the study.

1984 Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor  
1985 not relating to a health product (ANSM):

1986 • **Emerging safety issue**

1987 Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product  
1988 under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical  
1989 trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

1990 For example, this concerns:

- 1991 • any clinically significant increase in the frequency of an expected serious adverse reaction;  
1992 • early termination or a temporary halt for safety reasons for a trial carried out in another country with  
1993 the same product (act or method) as the one being studied in France;  
1994 • suspected unexpected serious adverse reactions in participants who have terminated the trial and of  
1995 which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.  
1996

1997 **10.2 The role of the investigator**

1998 **For each adverse event, the investigator must assess its severity** and report all serious and non-serious  
1999 adverse events in the case report form (e-CRF).

2000 The investigator must **document** serious adverse events **as thoroughly as possible** and provide a  
2001 definitive medical diagnosis, if possible.

2002 The investigator must **assess the intensity** of the adverse events by using general terms:

- 2003 ○ *Mild: tolerated by the patient, does not interfere with daily activities*  
2004 ○ *Moderate: sufficiently uncomfortable to affect daily activities*  
2005 ○ *Serious: prevents daily activities.*  
2006 ○

2007 The investigator must **assess the causal relationship between** a serious adverse events and strategies  
2008 investigated by the study.

2009

2010 The method used by the investigator is based on the WHO Uppsala Monitoring Centre Method), and uses  
2011 the following 4 causality terms:

- 2012 • Certain
- 2013 • Probable/likely
- 2014 • Possible
- 2015 • Unlikely (not excluded)

2016 Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version  
2017 dated 17/04/2012).

2018 Table: WHO-UMC : causality categories

Causality term	Assessment criteria*
<b>Certain to occur</b>	<ul style="list-style-type: none"> <li>· Event or laboratory test abnormality, with plausible time relationship to drug intake**</li> <li>· Cannot be explained by disease or other drugs</li> <li>· Response to withdrawal plausible (pharmacologically, pathologically)</li> <li>· Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)</li> <li>· Rechallenge satisfactory, if necessary</li> </ul>
<b>Probable/Likely</b>	<ul style="list-style-type: none"> <li>· Event or laboratory test abnormality, with reasonable time relationship to drug intake**</li> <li>· Unlikely to be attributed to disease or other drugs</li> <li>· Response to withdrawal clinically reasonable</li> <li>· Rechallenge not required</li> </ul>
<b>Possible</b>	<ul style="list-style-type: none"> <li>· Event or laboratory test abnormality, with reasonable time relationship to drug intake**</li> <li>· Could also be explained by disease or other drugs</li> <li>· Information on drug withdrawal may be lacking or unclear</li> </ul>
<b>Unlikely</b>	<ul style="list-style-type: none"> <li>· Event or laboratory test abnormality, with a time to drug intake**</li> <li>· that makes a relationship improbable (but not impossible)</li> <li>· Disease or other drugs provide plausible explanations</li> </ul>

2019 \*All points should be reasonably complied with

2020 \*\*Or study procedures

2021

### 2022 10.2.1 Serious adverse events that do not require the investigator to notify the 2023 sponsor without delay

2024

2025 A serious adverse event is any untoward medical occurrence that:

- |   |
|---|
| <ul style="list-style-type: none"> <li>2026 6- results in death</li> <li>2027 7- is life-threatening to the participant enrolled in the study</li> <li>2028 8- requires hospitalisation or prolongation of existing hospitalisation</li> <li>2029 9- results in persistent or significant disability/incapacity</li> <li>2030 10- is a congenital anomaly/birth defect</li> </ul> |
|---|

2031

### 2032 10.2.2 Specific features of the protocol

- 2033 • Adverse events deemed “medically significant”
- 2034 - Thrombotic and bleeding events

2035

2036 Serious adverse events that do not require the investigator to notify the sponsor without delay

- 2037 • These serious adverse events are only recorded in the case report forms; a data retrieval of the  
2038 case report forms will be implemented for serious adverse events every 60 patients. The



2039 primary objective of the trial is to assess the efficacy of anticoagulation strategies in reducing  
2040 the mortality and the time to clinical improvement in patients with severe COVID-19. Severe  
2041 COVID-19 also has a significant mortality rate. Thrombotic and bleeding events are secondary  
2042 endpoints.

2043

- 2044 • Deaths, and episodes of thrombosis and bleeding, do not need to be notified to the sponsor  
2045 without delay but will be recorded in the case report form. A CRF extraction of all deaths, and  
2046 episodes of thrombosis and bleeding will be realized every 60 inclusions. Thrombotic and  
2047 bleeding events will be adjudicated by an independent Adjudication committee every 60  
2048 inclusions.

2049

### 2050 **10.3 Role of the adjudication committee**

#### 2051 **10.3.1 Analysis and declaration of thrombotic and bleeding events, as well as serious** 2052 **adverse events**

2053 The adjudication committee assesses:

- 2054 - thrombotic and bleeding events
- 2055 - the **seriousness** of all the adverse events reported
- 2056 - the **causal relationship** with each specific strategy tested by the study,  
2057 All serious adverse events which the investigator and/or the adjudication committee believe could  
2058 have a causal relationship with the strategy tested
- 2059 - the **expected or unexpected nature** of the serious adverse reactions  
2060 Any serious adverse reaction is considered to be unexpected when the nature, severity or  
2061 progression are not consistent with information pertaining to the strategies tested.

2062

2063 **Serious adverse events** likely to be related to the strategies tested :

2064 - *major bleeding events*

2065 - *life threatening bleeding events*

2066

2067 The sponsor must notify all the investigators involved about any information that could adversely affect the  
2068 safety of the research participants.

#### 2069 **10.3.2 Analysis and declaration of other safety data**

2070 Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new  
2071 data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications  
2072 in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend  
2073 or halt or modify the study protocol or similar studies.

2074 The adjudication committee will inform the sponsor without delay upon knowledge of any emerging safety  
2075 issues.

2076 The sponsor will inform the competent authority and the Research Ethics Committee without delay upon  
2077 knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

2078 Following the initial declaration of any emerging safety issues, the sponsor will address to competent  
2079 authorities any additional relevant information about the emerging safety issue in the form of a follow-up  
2080 report, which must be sent no later than 7 days from learning of the information.

## 2081 **11 Specific study committees**

### 2082 **11.1 Steering committee**

2083

2084 The trial steering committee (TSC) will oversee the overall conduct of the trial. The TSC will make  
2085 recommendations regarding all trial-related decisions.

2086 Members:

2087 - principal investigator (Dr Vincent LABBE),

2088 - scientific supervisor (Pr Armand MEKONTSO DESSAP),

2089 - biostatistician (Pr Etienne AUDUREAU),

2090 - the sponsor's appointed representatives for the trial: Clinical Research Associate in charge of the project  
2091 and project manager URC DRCI (URC des Hôpitaux Universitaires Henri Mondor) and project manager of  
2092 the DRCI promotion unit.

2093 Role:

2094 - Define the overall structure of the study, coordinate information, determine the initial methodology and  
2095 oversee the trial.

2096 - Propose procedures to be followed during the study, acknowledging any recommendations from the  
2097 Steering Committee.

### 2098 **11.2 Adjudication committee**

2099 An adjudication committee will independently adjudicate the thrombotic and bleeding events during the  
2100 trial, as well as the serious adverse events.

2101 Members:

2102 - Pr Nadia AISSAOUI

2103 - Dr Mathieu SCHMIDT

2104

2105 Role:

2106 - Review and adjudicate reported thrombotic and bleeding events, as well as deaths and serious adverse  
2107 events

2108 - The committee will meet after every 60 inclusions in the study.

2109

## 2110 **12 data management**

### 2111 **12.1 Data collection procedures**

2112

2113 Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in  
2114 collaboration with URC-MONDOR.

2115

2116 **12.2** Identification of data recorded directly in the CRFs which will be considered as source data

2117

2118 Vital status at Day-28 and Day-90, unless the patient is still hospitalized and EQ5D5L.

2119

2120 **12.3** Right to access data and source documents

2121

2122 12.3.1 Data access

2123

2124 In accordance with GCPs:

2125 - the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to  
2126 all locations where the study will be carried out, the source data, the source documents and the reports, for  
2127 the purposes of the sponsor's quality control and audit procedures.

2128 - the investigators will ensure the persons in charge of monitoring, quality control and auditing the research  
2129 have access to the documents and personal data strictly necessary for these tasks, in accordance with the  
2130 statutory and regulatory provisions in force

2131 12.3.2 Source documents

2132

2133 Source documents are defined as any original document or item that can prove the existence or accuracy of  
2134 a data or a fact recorded during the study. These documents will be kept by the investigator, or by the  
2135 hospital in the case of a hospital medical file, for 15 years.

2136 12.3.3 Data confidentiality

2137

2138 The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé*  
2139 *Publique* (French Public Health Code) will take all necessary precautions to ensure the confidentiality of  
2140 information relating to the study, the study participants and in particular their identity and the results  
2141 obtained.

2142 These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance  
2143 with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).

2144 During and after the research involving human participants, all data collected concerning the participants  
2145 and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-  
2146 identifying.

2147 Under no circumstances shall the names and addresses of the participants involved be shown. Only the  
2148 participant's initials will be recorded, accompanied by an encoded number specific to the study indicating  
2149 the order of enrolment.

2150 The sponsor will ensure that each participant has given written permission for any personal information  
2151 about him or her which is strictly necessary for the quality control of the study to be accessed.

2152 **12.4** Data processing and storage of research documents and data  
2153

2154 12.4.1 Identification of the data processing manager and location(s)  
2155

2156 Data management and statistical analysis will be performed by URC-MONDOR.

2157 12.4.2 Data entry

2158 Non-identifying data will be entered electronically via a web browser.  
2159  
2160

2161 **12.5** Data ownership  
2162

2163 AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior  
2164 permission.

2165 **13** statistical aspects

2166 **13.1** Proposed statistical methods, including the timetable for any planned interim analyses

2167 All statistical analyses will be conducted after data review and freezing of data base, using Stata v16.1  
2168 (StataCorp, College Station, TX, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna,  
2169 Austria), within the Henri Mondor Clinical Research Unit (URC) under the supervision of Pr Etienne  
2170 Audureau.

2171

2172 *Descriptive analyses*

2173 Descriptive statistical analyses will be conducted overall and regarding the randomized groups in terms of  
2174 general characteristics, demographics, history and baseline characteristics, as well as numbers of  
2175 prematurely study treatment withdrawals. Quantitative variables will be presented as mean ( $\pm$ standard  
2176 deviation) or median (25-75th percentiles) according to the normality of their distribution as assessed by  
2177 means of Shapiro-Wilk tests and graphical methods, and qualitative variables will be presented as numbers  
2178 (%).

2179

2180 *Primary endpoint analysis*

2181 The prespecified primary end point will be a ranked composite score that incorporates death and the time  
2182 to clinical improvement, calculated in such manner that death constitutes a worse outcome than more days  
2183 to clinical improvement. Each patient will be compared with every other patient in the study and assigned a  
2184 score (tie: 0, win: +1, loss: -1) for each pairwise comparison based on whom fared better. If one patient  
2185 survived and the other did not, scores of +1 and -1 will be assigned, respectively, for that pairwise  
2186 comparison. If both patients in the pairwise comparison survived, the assigned score will depend on which  
2187 patient had more days to clinical improvement: the patient with fewer days will receive a score of +1,  
2188 while the patient with more days will receive a score of -1. If both patients survived and had the same

2189 number of days to clinical improvement, or if both patients died, they both will be assigned a score of 0 for  
2190 that pairwise comparison. For each patient, scores for all pairwise comparisons will be summed, resulting  
2191 in a cumulative score for each patient. These cumulative scores will be ranked and compared between  
2192 treatment groups via a non-parametrical Mann-Whitney test.

2193 No interim analysis is planned. The primary efficacy endpoint will be analyzed using the intention to treat  
2194 (ITT) population. Supportive analyses in the per protocol (PP) population will be carried out, so as to  
2195 document the patients excluded from PP, investigate the impact on ITT analysis and eventually check  
2196 whether similar results are obtained for a robust interpretation. All analyses of secondary endpoints will be  
2197 conducted on both ITT and PP populations to assess the robustness of the results.

2198

### 2199 *Secondary endpoints*

2200 Comparisons between randomized groups at given timepoints will be conducted by use of the Chi square  
2201 test or the Fisher's exact test, according to expected numbers in crossings, for categorical variables and by  
2202 use of t-tests or non-parametrical Mann-Whitney tests (pairwise comparisons), and ANOVA or Kruskal  
2203 Wallis tests (global comparisons for >2 groups) for quantitative variables, as appropriate. Pairwise  
2204 comparisons within groups (i.e. across timepoints) will be conducted using tests for paired data, i.e.  
2205 McNemar tests for qualitative data, and t-tests for paired data or Wilcoxon signed ranks tests for  
2206 continuous data, as appropriate.

2207 Individual components of the composite primary endpoint will be assessed as secondary endpoints, i.e. all-  
2208 cause mortality at 28-day follow-up and number of days until clinical improvement. To do so, methods for  
2209 time-to-event endpoints based on follow-up censored data will be conducted, accounting for the competing  
2210 risks of hospital discharge (for mortality evaluation) and death (for time to clinical improvement). Kaplan-  
2211 Meier survival curves and cumulative incidence curves will be plotted for each treatment group, and Fine-  
2212 Gray regression models will be used to calculate subhazard ratios along with their 95% confidence  
2213 intervals and corresponding P-values.

2214 Analyses of independent determinants of quantitative secondary endpoints will be performed using  
2215 multivariate linear regression analyses adjusting for baseline characteristics and, for global longitudinal  
2216 analysis using generalized linear regression mixed models, testing interaction between time, group and  
2217 prespecified predictors and entering patient level as a random effect to account for the hierarchical  
2218 structure of repeated data.

2219

2220 Tolerance analysis will be carried out according to the period of appearance and randomization group on  
2221 the detailed adverse events relating to the treatment, comparing the rates of occurrence and time of  
2222 occurrence.

2223

### 2224 **13.2 Hypotheses for calculating the required number of participants, and the result**

2225

2226 The required number of participants is **300 patients randomized (353 patients included)**.

2227 Using estimates derived from prior studies led in similar study populations<sup>15</sup>, a sample of at least 300  
2228 patients (100 per group) was estimated to provide  $\geq 80\%$  power to detect a statistically significant  
2229 difference in the primary ranked composite outcome with 2-sided alpha of 0.017 using a Bonferroni  
2230 correction for multiple testing considering 3 pairwise comparisons between randomized arms. Sample size  
2231 calculations assumed 28-day mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/- 3

2232 days (standard deviation), 14 days and 12 days, with LD-PA, HD-PA, and TA, respectively. We  
2233 hypothesize a 15% rate of positive CTPA<sup>16,17</sup>. In order to randomize 300 patients, we aim at including 353  
2234 patients.

2235 In detail, the sample size calculation was carried out by considering pairwise comparisons between the  
2236 groups. For each comparison performed, 5000 samples were simulated using R software.

2237 For the first component of the hierarchical primary endpoint (i.e. mortality), survival curves were  
2238 simulated based on a Weibull distribution using the R package *simsurv*.

2239 For the second component of the hierarchical primary endpoint (i.e. days until clinical improvement)  
2240 assessed in alive patients, two different approaches were used regarding the distribution of this parameter  
2241 to test the robustness of the results depending on retained hypotheses. First, a normal distribution was  
2242 hypothesized with means $\pm$ SD of 16 $\pm$ 3, 14 $\pm$ 3 and 12 $\pm$ 3 days in LD-PA, HD-PA and TA,  
2243 respectively. Second, incidence curves for clinical improvement were simulated based on a Weibull  
2244 distribution using the R package *simsurv*, with survival medians of 16, 14 and 12 days in LD-PA, HD-PA  
2245 and TA, respectively.

2246 For both approaches, a systematic 5% rate of patients were identified through simulation as alive patients  
2247 at D28 but without achieving clinical improvement, consistent with Cao et al 2020<sup>15</sup>. Standard deviation  
2248 and mean number of days until clinical improvement, as well as shape and scale parameters for the  
2249 Weibull survival curves simulations were determined from Cao et al 2020<sup>15</sup>, considering median  
2250 [interquartile range] survival times and Kaplan Meier curves.

2251 Within each sample/pairwise comparison, each patient's score was calculated based on comparing each  
2252 patient in one group to all patients in the second group (23). These scores were then compared between  
2253 groups by a Mann-Whitney / Wilcoxon test in each of the 5000 samples and the p-value of each test  
2254 recorded. For each pairwise comparison, the proportion of tests with a p-value <0.017 was calculated,  
2255 providing an estimate for the statistical power achieved.

2256

2257 **13.3 State whether subjects who exit the study prematurely will be replaced and in what**  
2258 **proportion.**

2259

2260 No participants who withdraw from or drop out of the study will be replaced.

2261

2262 **13.4 Anticipated level of statistical significance**

2263 The analysis of the composite primary endpoint will rely on a 1.7% bilateral alpha risk, using a Bonferroni  
2264 correction for multiple testing considering 3 pairwise comparisons between randomized arms. A bilateral  
2265 alpha of 5% will be used for all comparisons relating to secondary endpoints. No other correction for test  
2266 multiplicity will be applied for the proposed study, to the exception of pairwise post-hoc comparisons  
2267 performed after significant global tests involving multicategorical variables.

2268

2269 **13.5 Statistical criteria for termination of the study**

2270 Not applicable.

2271

2272 **13.6 Method for taking into account missing, unused or invalid data**

2273 All missing or invalid data will be systematically checked and searched for in patients' medical  
2274 records. In addition to complete case analyses based on available data, sensitivity analyses will be  
2275 led considering missing values for the primary endpoint as strategy failures, regardless of the  
2276 strategy, or using approaches based on multiple imputation by chained equations methodology.  
2277

### 2278 **13.7 Management of modifications made to the analysis plan for the initial strategy.**

2279 Any modification of the original statistical analysis plan (as described in the study protocol or in the  
2280 statistical analysis plan) will be described and justified in a protocol amendment and/or in the clinical study  
2281 reports.  
2282

### 2283 **13.8 Selection of populations**

2284 Intention to treat (ITT) population will be defined as patients having signed the consent form to enter the  
2285 study and having been randomized to one of the assessed arms. ITT population will thus be analyzed  
2286 according to their initial randomized group.

2287 Per protocol (PP) population will be defined as patients having been randomized and without any major  
2288 deviation to the protocol, including: non-respect of all selection criteria, non-respect of the randomized  
2289 treatment allocation and/or duration (wrong strategy received, premature discontinuation of treatment –  
2290 except for death), missing data for the primary efficacy endpoints, inclusion in another interventional  
2291 study, major protocol deviation identified during a blinded data review before data base freezing.

2292 In case of consent withdrawal, only data collected before withdrawal will be used.  
2293

## 2294 **14 QUALITY CONTROL AND ASSURANCE**

### 2295 **14.1 General organisation**

2296

2297 The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study.  
2298 The sponsor must implement a quality assurance system to best monitor the implementation of the study in  
2299 the investigation centres.

2300 For this purpose, the sponsor will define a strategy for opening the centers and may, if necessary, set up a  
2301 quality control of the data.

#### 2302 14.1.1 Strategy for opening the centres

2303 The strategy for opening the centres will be determined before the research begins.

#### 2304 14.1.2 Data quality control

2305

2306 For this Minimal Risks and Burden research study, the appropriate quality control level has been  
2307 determined based on the impact and the budget of the research. The sponsor, working in liaison with the  
2308 coordinating investigator, will determine this level before the research begins.

2309 A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good  
2310 completion of the study, for collecting, documenting, recording and reporting all handwritten data, in  
2311 accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation  
2312 Department.

2313 The investigator and the members of the investigator’s team agree to make themselves available during  
2314 regular Quality Control visits carried out by the Clinical Research Associate.

#### 2315 **14.2 Case report forms**

2316

2317 The case report forms should only contain the data needed to analyse the study and publish the results. All  
2318 other data needed to monitor the participants during and outside of the study are recorded in the medical  
2319 file.

2320 All information required by the protocol must be entered in the case report forms. The data must be  
2321 collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data  
2322 must be coded.

2323 Every site will have access to the electronic case report forms via a web-based data collection system.  
2324 Investigators will be given a document offering guidance on using this tool.

2325 When the investigators complete the case report form via the Internet, the CRA can view the data quickly  
2326 and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered.  
2327 In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this  
2328 end, the investigator must validate any changes to the values in the case report form. An audit trail will be  
2329 kept of all changes. A justification can be added when applicable, as a comment.

2330 A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study.  
2331 The original of this document will be archived by the sponsor. The investigator must archive a copy of the  
2332 authenticated document that was issued to the sponsor.

2333

2334

#### 2335 **14.3 Management of non-compliances**

2336

2337 Any events that occur as a result of non-compliance – by the investigator or any other individual involved  
2338 in running the study – with the protocol, standard operating procedures, good clinical practices or statutory  
2339 and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

2340 These non-compliances will be managed in accordance with the sponsor's procedures.

2341

#### 2342 **14.4 Audit**

2343

2344 The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the  
2345 inspections carried out by the competent authorities. All data, documents and reports may be subject to  
2346 regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

2347 An audit can be carried out at any time by individuals appointed by the sponsor and independent of those  
2348 responsible for the research. The aim of the audit is to ensure the quality of the study, the validity of the  
2349 results and compliance with the legislation and regulations in force.

2350



2351 The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.  
2352 The audit may encompass all stages of the study, from the development of the protocol to the publication  
2353 of the results, including the storage of the data used or produced as part of the study.  
2354

#### 2355 **14.5** Principal Investigator's commitment to assume responsibility

2356

2357 Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated  
2358 personal *curriculum vitae*, signed and dated less than one year, with his/her RPPS number (Répertoire  
2359 Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include  
2360 any previous involvement in clinical research and related training.

2361

2362 Each investigator will commit to comply with legislation and to conduct the study in line with regulations,  
2363 in accordance with the Declaration of Helsinki.  
2364

2365 The Principal Investigator at each participating center will sign a commitment of responsibility (standard  
2366 DRCI document) which will be sent to the sponsor's representative. In this study, a Principal Investigator  
2367 will be declared for each COVID center, grouping multiple participating department and COVID units  
2368 within a hospital in accordance with the specific care of COVID patients as well as organizational changes  
2369 related to the scale of the pandemic.

2370 The investigators and their staff will sign a delegation of duties form specifying each person's role and will  
2371 provide their CVs.  
2372

## 2373 **15** ETHICAL AND LEGAL CONSIDERATIONS

### 2374 **15.1** Methods for informing research participants and obtaining their consent

2375

2376 In accordance with Article L.1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no  
2377 research involving human participants with minimal risks and burden can be carried out on a person  
2378 without his/her freely given and informed consent, obtained expressly after the person has been given the  
2379 information specified in Article L.1122-1 of the aforementioned Code.

2380

2381 The necessary reflection period is given to the individual between the time when he or she is informed and  
2382 when he or she signs the consent form.

2383

2384 The person's freely-given written informed consent will be obtained by the principal investigator, a  
2385 physician representing the investigator or a qualified person, before the person is enrolled on the study.

2386

2387 A copy of the information note and consent form, signed and dated by the research participant and by the  
2388 principal investigator, the physician representing the investigator or a qualified person, will be given to the  
2389 individual prior to their participation in the study. The principal investigator or the physician representing  
2390 him/her will keep a copy.

2391

2392 At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the  
2393 consent forms. This envelope will be archived by the sponsor.

2394

2395 In addition, the investigator will specify in the person's medical file the person's participation in the  
2396 research, the procedures for obtaining his/her consent or consent from any other person in the cases set  
2397 forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code),  
2398 as well as the methods used for providing information for the purpose of collecting it. The investigator will  
2399 retain one copy of the signed and dated consent form.

2400

2401 Special circumstances: If the person is physically unable to give his or her written consent, consent may be  
2402 witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative.  
2403 These persons must have be fully independent of the investigator and of the sponsor.

2404

2405 Emergency procedure: If the person is unable to express his will and his/her legally acceptable  
2406 representative is unidentified and/or unreachable at time of inclusion, the investigator may proceed to the  
2407 inclusion of the person without any consent. The investigator must supply any document demonstrating  
2408 that he has extensively tried to identify and/or to reach the legally acceptable representative. In this case of  
2409 emergency procedure, his/her legally acceptable representative gives his consent as soon as he is identified  
2410 and reachable; the person gives his consent to continue his participation to the study when he has recovered  
2411 his ability to express his will.

2412

2413 In practice, the consent will be obtained as follows:

2414 1/ If the patient is capable of participating in the consent process, the investigator will obtain a written  
2415 consent from the patient after an appropriate explanation.

2416 2/ If the patient is unable to give their consent, the investigator will obtain a written consent from his/her  
2417 legally acceptable representative (Article L.1122-2 CSP). As soon as the patient will be capable of  
2418 participating in the consent process, he will be given full information about the study and the investigator  
2419 will obtain a continuation consent from the patient.

2420 3/ If the patient is not capable of participating in the consent process, and his/her legally acceptable  
2421 representative is not present at the time of selection criteria fulfillment, the patient will be included in  
2422 emergency situation (article L1122-1-3 of CSP). The patient or, where applicable, the members of the  
2423 family or the person of trust mentioned in Article L. 1111-6 shall be informed as soon as possible and their  
2424 consent shall be sought from them for the possible continuation of such research. They may also object to  
2425 the use of personal data in the context of this research.

2426

2427 The use of an emergency inclusion in last resort is justified by the following arguments : i) severe COVID-  
2428 19 is a life-threatening situation with a high risk of mortality ; ii) in order to improve patient outcome, an  
2429 anticoagulation heart rate control should be initiated as early as possible after septic shock onset.

2430

2431 **15.2 Prohibition from participating in another clinical study or exclusion period after the study, if**  
2432 **applicable**

2433

2434 Whilst participating in this trial, subjects may not take part in any other interventional clinical study on  
2435 anticoagulation of COVID-19 pneumonia.

2436 **15.3** Compensation for participants  
2437

2438 15.3.1 Reimbursement of expenses **incurred**  
2439

2440 Not applicable.  
2441

2442 15.3.2 Compensation  
2443

2444 There will be no compensation.  
2445

2446 **15.4** Registration on the national register of study participants to studies involving human participants  
2447

2448 Not applicable.  
2449

2450 **15.5** Legal obligations  
2451

2452 Assistance Publique-Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI  
2453 (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article  
2454 L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique-Hôpitaux de  
2455 Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case,  
2456 notification will be sent to the investigator.

2457

2458

2459 **15.6** Request for approval from the CPP (Research Ethics Committee)  
2460

2461 Prior to starting the study, AP-HP, as sponsor, must obtain approval from the CPP (Research Ethics  
2462 Committee) for its Minimal Risks and Burden research study, within the scope of the committee's authority  
2463 and in accordance with in force legislation and regulatory requirements.

2464

2465 **15.7** Informing the ANSM  
2466

2467 AP-HP will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol  
2468 to the ANSM for information.

2469

### 2470 **15.8** Procedures relating to data protection regulations

2471

2472 The computer file used for this research is implemented in accordance with French (amended  
2473 “Informatique et Libertés” law governing data protection) and European (General Data Protection  
2474 Regulation – GDPR) regulations.

2475 This research is not governed by the CNIL “Reference Method” (MR-001) because of the possible  
2476 inclusion due to an emergency situation without collection of consent at the time of inclusion. The sponsor  
2477 must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data  
2478 processing involving the data required to conduct the research.

2479

### 2480 **15.9** Amendments to the research

2481

2482 Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor  
2483 for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics  
2484 Committee) before the amendment can be implemented.

2485 The information note and the consent form can be revised if necessary, in particular in case of a substantial  
2486 amendment to the study or if adverse reactions occur.

2487

### 2488 **15.10** Final study report

2489

2490 The final report for the research involving human participants referred to in Article R1123-67 of the *Code*  
2491 *de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the  
2492 investigator. A report summary drafted according to the reference plan of the competent authority must be  
2493 sent to the competent authority within a period of one year following the end of the study, i.e., the end of  
2494 the participation of the last participant in the study

2495

### 2496 **15.11** Archiving

2497

2498 Specific documents for a research involving human participants with Minimal Risks and Burden are to be  
2499 archived by the investigator and the sponsor for 15 years following the end of the research.

2500 This indexed archiving includes, in particular:

- 2501 - A sealed envelope for the investigator containing a copy of all the information notes and consent forms
- 2502 signed by all individuals at the centre who participated in the study;

- 2503 - A sealed envelope for the sponsor containing a copy of all the information notes and consent forms  
2504 signed by all individuals at the centre who participated in the study;
- 2505 - Study binders for the investigator and the sponsor, including (non-exhaustive list):
- 2506 • the successive versions of the protocol (identified by the version number and its date), and any  
2507 appendices
  - 2508 • decisions of the CPP (Research Ethics Committee)
  - 2509 • any correspondence
  - 2510 • the enrolment list or register
  - 2511 • the appendices specific to the research
  - 2512 • final study report
- 2513 - Data collection documents  
2514

## 2515 **16 Funding and Insurance**

### 2516 **16.1 Funding sources**

2517 LEO Pharma

### 2518 **16.2 Insurance**

2519

2520 For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own  
2521 public liability, as well as the public liability for all the physicians involved in the study. The sponsor will  
2522 also provide full compensation for any damages caused by the study to the participant enrolled and their  
2523 beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator.  
2524 Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the  
2525 person who initially consented to participate in the study.

2526 Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE  
2527 through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of  
2528 any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la  
2529 Santé Publique (French Public Health Code).

2530

## 2531 **17 Publication rules**

2532 The author(s) of any publication relating to this study must name the sponsor AP-HP (DRCI) and the  
2533 source of funding.

2534

2535 **This study has been registered on the website <http://clinicaltrials.gov/> under number 04808882.**  
2536

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2637

2638 **19 List of addenda**

2639



2640

19.1 Annex 1: Prevention and treatment of thrombosis in hospitalized patients with COVID-19 <sup>7</sup>

	No oxygen therapy	Oxygen therapy	High flow nasal oxygen therapy or mechanical ventilation	Monitoring of anticoagulant treatment
BMI <30 kg/m <sup>2</sup>	<b>LMWH with standard prophylactic dose or fondaparinux</b> (e.g. enoxaparin 4000 IU/24h SC; or 2000 IU/24h SC if Clcr between 15 and 30 ml/min; tinzaparin 3500 IU/24h SC if Clcr >20 ml/min; dalteparin 5000 IU/24h SC si si Clcr >30 ml/min fondaparinux 2.5 mg/24h if Clcr >50 ml/min)			<b>Monitoring of anti-Xa activity:</b> - LMWH: avoid overdose (maintain anti-Xa < 1.2 IU/ml for enoxaparin) - UFH: target 0.3-0.5 IU/ml (+ platelet count every 48 hours)
BMI ≥30 kg/m <sup>2</sup> <u>Without</u> other thrombotic risk factor* BMI ≥30kg/m <sup>2</sup> <u>with</u> thrombotic risk factor*	enoxaparin 4000 IU/12h SC enoxaparin 6000 IU/12h SC if weight >120 kg UFH: 200 IU/kg/24h, if Clcr < 30 ml/min.			
Iterative catheter or renal filter thrombosis Severe Inflammatory Syndrome (e.g. fibrinogen >8 g/L) Hypercoagulability (e.g. D-dimers >3.0 µg/ml) ECMO Long-term anticoagulant treatment	LMWH at curative dose e.g. enoxaparin 100 IU/kg/12h SC (actual weight), without exceeding 10,000 IU/12h. UFH 500 IU/kg/24h if Clcr <30 ml/min Re-evaluate the dose in case of multiorgan failure or consumption coagulopathy.			<b>Monitoring of anti-Xa activity:</b> - LMWH: avoid overdose (maintain anti-Xa < 1.2 IU/ml for enoxaparin) - UFH: target 0.5-0.7 IU/ml (+ platelet count every 48 hours)

Intermediate risk
High risk
Very high risk  
 NB: Low risk is not covered.

\*ThromboEmbolic Risk Factors : active cancer, recent personal history of thrombosis...  
 Clcr : Creatinine clearance; LMWH: low molecular weight heparin; UFH: unfractionated heparin

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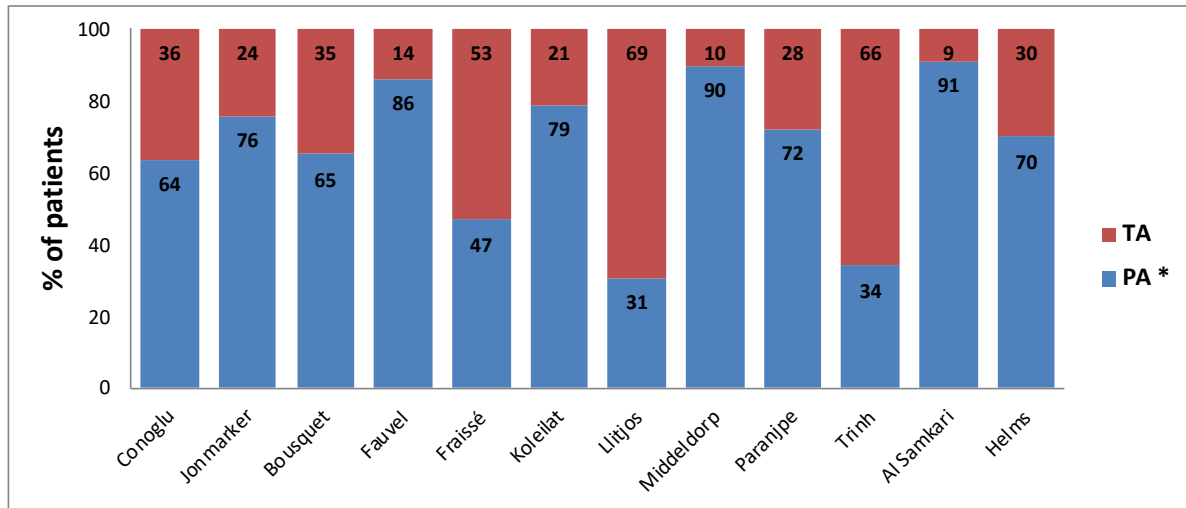
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**19.2** Annex 2: main observational studies reporting the strategies of anticoagulation used in usual practice in hospitalized patients with COVID-19 usual practice about strategy of anticoagulation



2649

2650

2651 Abbreviations: TA, therapeutic anticoagulation ; PA, preventive anticoagulation

2652 \*including « low dose » and « high dose » preventive anticoagulation

2653 Reference: <sup>4,12,13,27-33</sup>

2654

2655

2656

2657 **19.3** Annex 3: sepsis-induced Coagulopathy Score <sup>34</sup>

2658

Variable		Points	2659
INR	≤1.2	0	2660
	>1.2 to 1.4	1	2661
	>1.4	2	2662
Platelet count, cells x 10 <sup>9</sup> /L	≥150	0	2663
	100 to <150	1	2664
	<100	2	2665
Total SOFA score*	0	0	2666
	1	1	2667
	≥2	2	2668

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2675 \*Summation of the SOFA score's respiratory, cardiovascular, hepatic, and renal SOFA components.

2676

2677

2678

2679 **19.4** : Annex 4: Quality of life questionnaire (EQ5D5L)

2680

Variable	Response (Please select the one sentence that best describes your health today ?)
<b>MOBILITY</b>	I have no problems in walking about I have slight problems in walking about I have moderate problems in walking about  I have severe problems in walking about I am unable to walk about
<b>SELF-CARE</b>	I have no problems washing or dressing myself I have slight problems washing or dressing myself I have moderate problems washing or dressing myself  I have severe problems washing or dressing myself I am unable to wash or dress myself
<b>USUAL ACTIVITIES</b> (e.g. work, study, housework, family or leisure activities)	I have no problems doing my usual activities  I have slight problems doing my usual activities I have moderate problems doing my usual activities  I have severe problems doing my usual activities I am unable to do my usual activities
<b>PAIN / DISCOMFORT</b>	I have no pain or discomfort I have slight pain or discomfort I have moderate pain or discomfort  I have severe pain or discomfort I have extreme pain or discomfort
<b>ANXIETY / DEPRESSION</b>	I am not anxious or depressed I am slightly anxious or depressed I am moderately anxious or depressed  I am severely anxious or depressed I am extremely anxious or depressed
<b>HEALTH TODAY</b>	We would like to know how good or bad your health is TODAY. The scale is numbered from 0 to 100 : 100 means the best health you can imagine ; 0 means the worst health you can imagine. Please tell me the number to indicate how your health is TODAY.

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Variable	Définition
<b>Thrombotic event</b>	
Ischemic stroke <sup>21</sup>	Acute focal cerebral, spinal, or retinal dysfunction associated with infarction on an imaging study (CT scan or MRI). Hemorrhagic conversion of an ischemic stroke should be classified as ischemic
Non-cerebrovascular arterial thrombotic event	Acute vascular occlusion of the extremities or any non-cerebrovascular organ by one or more of the following: standard clinical and laboratory testing, operative findings, or autopsy findings <sup>21</sup>
Deep venous thrombosis (DVT)	Confirmed by venous duplex compression ultrasonography or CT-scan <sup>22</sup>
Pulmonary emboli	Venous thromboembolism in pulmonary arteries identified on CT scan
Central venous catheter (CVC)-related DVT	DVT confirmed by venous duplex compression ultrasonography or CT-scan in association with the CVC or confirmed within 5 days of CVC removal
<b>Bleeding event</b>	
Major bleeding event (ISTH definition, <sup>23</sup> )	Meets $\geq 1$ of the following criteria: <ul style="list-style-type: none"> <li>- symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome;</li> <li>- bleeding associated with a reduction in hemoglobin of <math>\geq 2</math> g/dl (1.24 mmol/l) or leading to transfusion of <math>\geq 2</math> U blood or packed cells ;</li> <li>- fatal bleeding.</li> </ul>
Life-threatening bleeding event (RE-LY definition <sup>24</sup> )	Meets $\geq 1$ of the following criteria: <ul style="list-style-type: none"> <li>- fatal bleeding;</li> <li>- symptomatic intracranial bleeding;</li> <li>- bleeding with a decrease in hemoglobin of <math>\geq 50</math> g/L, or bleeding requiring transfusion of <math>\geq 4</math> units of blood; necessitating surgical, endoscopic, or endovascular action;</li> </ul>
Intracranial bleeding (ISTH Definition, <sup>23</sup> )	Intracerebral bleedings, subdural bleedings, epidural bleedings or subarachnoid bleedings.
Fatal bleeding (ISTH Definition, <sup>23</sup> )	Bleeding event that is the primary cause of death or contributes directly to death.

2685 Abbreviations: ISTH, International Society on Thrombosis and Haemostasis; RE-LY, Randomized Evaluation of Long-Term  
 2686 Anticoagulation Therapy.

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2688 **19.6 Annex 6: List of Investigators**

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#### 4 Protocol summary of changes

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2693 The original version of the protocol, version 1.1 was issued on 22/03/2021.

2694 Below are the amendments to the protocol, their rationale and summary of changes.

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#### 2696 **Amendment 1 to the Protocol – Version 2.0 of 15/04/2021**

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Concerned section	Initial text	Modified/added text	Rationale
<p><b>Summary:</b> Exclusion criteria</p> <p>7.2 Exclusion criteria</p>	Need for therapeutic anticoagulation	Need for therapeutic anticoagulation ( <i>except for COVID-related pulmonary thrombosis</i> );	Clarification regarding the exclusion criterion "therapeutic anticoagulation", which does not concern patients who had pulmonary artery thrombosis secondarily to COVID; such patients are included in the study but not randomised (ancillary study).
<p><b>Summary:</b> Interventions or product under investigation</p> <p>6.1.2 Inclusion visit</p> <p>6.2 Table or diagram summarising the chronology of the study, with distinction between standard</p>	A CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion.	A CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion. <i>If a CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis was deemed unchanged by the clinician, the result of that CTPA may be considered at time of inclusion.</i>	<p>Clarification on CTPA.</p> <p>If a CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis was deemed unchanged by the clinician, the result of that CTPA may be considered as inclusion data.</p> <p>This strategy aims to</p>



care and research			spare patients unnecessary re-exposure to radiation and contrast agents.
<p><b>Summary:</b> Interventions or product under investigation</p> <p>2.4 Interventions and products which will be performed or used as standard</p>	<p>Participants randomised to the LD-PA, HD-PA, and TA strategies will receive low molecular weight heparin (LMWH), tinzaparin whilst taking into account its contraindications, recommended dose ranges, and monitoring if applicable, as follows: LD-PA: 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h.</p>	<p>Participants randomised to the LD-PA, HD-PA, and TA strategies will receive low molecular weight heparin (LMWH), tinzaparin whilst taking into account its contraindications, recommended dose ranges, and monitoring if applicable, as follows: LD-PA: 3500 IU/24h; HD-PA: 7000 IU/24h; TA: 175 IU/kg/24h. <i>The participating centres are allowed to use their available tinzaparin pre-filled syringe type, e.g. a 4000 IU/24h dose instead of the 3500 IU/24h in the LD-PA group given their similar indication in that regimen.</i></p>	<p>Clarification of tinzaparin doses in low-dose prophylactic anticoagulation strategy. The participating centres were allowed to use their available tinzaparin pre-filled syringe type, e.g. a 4000 IU/24h dose instead of the 3500 IU/24h in the LD-PA group given their similar indication in that regimen</p>
<p><b>Summary</b></p> <p>Number of centres</p> <p>5.2 Number of participating sites</p> <p>7.3 Recruitment procedure</p> <p>Annex 6: List of investigators</p>	<p>24</p> <p>This is a multicentre research in which 24 university-affiliated hospitals would like to participate.</p> <p>Number of centres: 24</p> <p>Number of participants/centre: 15</p>	<p>26 recruiting hospitals in France.</p> <p>This is a multicentre research in which 26 university-affiliated hospitals would like to participate.</p> <p>Number of centres: 26</p> <p>Number of participants/centre: 13 to 14</p> <p><i>Dr William JUGUET</i> <i>william.juguet@aphp.fr</i></p>	<p>Given the dynamics of the epidemic, we aimed to increase our recruitment potential to 26 centres</p>

		<p><i>CH Avicenne – Jean Verdier AP-HP, Hôpitaux Universitaires Paris-Seine- Saint-Denis, Bondy France</i></p> <p><i>Réanimation et autres unités du centre COVID</i></p> <p><i>CH Louis-Mourier AP-HP. Nord - Université de Paris, Colombes France</i></p> <p><i>Médecine Intensive Réanimation et autres unités du centre COVID</i></p>	
7.3 Recruitment procedure		<p><i>It is a national multicentre study.</i></p> <p><i>Recruitment of patients will be conducted in various departments of selected hospital centres as well as in various “COVID” units that will be created according to the organisation of each hospital. These departments and units will be unified in a single “COVID centre” in each hospital.</i></p> <p><i>In each hospital, assigned investigators are likely to recruit and follow patients in that “COVID centre”.</i></p>	<p>Clarification of the recruitment procedure. Given the dynamics of the epidemic, "COVID" units have been created to facilitate cohorting of COVID patients within the hospitals. However, this organisation does not always correspond to a classical routine "department". For such, the work of the various units and departments dedicated to manage COVID patients are united into "COVID Centres" inside the hospital. In compliance with good practice, we wished that the investigators assigned within each hospital could recruit and follow the patients in all units or departments of their "COVID Centre", within the respect of the current clinical</p>
14.5 Principal Investigator's commitment to undertake responsibility	<p>[...]</p> <p>The Principal Investigator of each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.</p> <p>The investigators and their staff will sign a</p>	<p>[...]</p> <p>The Principal Investigator of each participating centre will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative. <i>In this study, a Principal Investigator will be nominated for each COVID centre; the latter regroups multiple participating departments and COVID units within a hospital in</i></p>	<p>In compliance with good practice, we wished that the investigators assigned within each hospital could recruit and follow the patients in all units or departments of their "COVID Centre", within the respect of the current clinical</p>

	delegation of duties form specifying each person's role, and should provide their CVs as well.	<i>accordance with the specific management plan of COVID patients as well as organisational changes undertaken to face the scale of the pandemic.</i>  The investigators and their staff will sign a delegation of duties form specifying each person's role, and should provide their CVs as well.	management.
Annexe 6: List of investigators	Service	<i>Centre COVID</i>	
	Médecine Intensive Réanimation	<i>Médecine Intensive Réanimation et autres unités du centre COVID</i>	
	Service de pneumologie et de soins intensifs respiratoires	<i>Service de pneumologie et de soins intensifs respiratoires et autres unités du centre COVID</i>	
	Service Réanimation/ Surveillance continue	<i>Service Réanimation/ Surveillance continue et autres unités du centre COVID</i>	
	Service de réanimation et unité de soins continus	<i>Service de réanimation et unité de soins continus et autres unités du centre COVID</i>	
	Réanimation polyvalente et unité de surveillance continue	<i>Réanimation polyvalente et unité de surveillance continue et autres unités du centre COVID</i>	

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2700 **Amendment 2 to the Protocol – Version 3.0 of 13/07/2021**

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Concerned section and page	Initial text	Modified/added text	Rationale
<p><b>Summary:</b> Schedule of the study</p> <p>6.1 Schedule of the study</p>	<p>Inclusion period: 6 months</p> <p>Total duration: 9 months</p>	<p>Inclusion period: 18 months</p> <p>Total duration: 21 months</p>	<p>Given the current dynamics of the epidemic and its uncertain nature, we wished to prolong our inclusion period by 12 months.</p>
<p><b>Summary:</b> Number of patient expected to be enrolled per site and per month</p> <p>7.3 recruitment procedure</p>	<p>2 to 3</p>	<p>1</p>	<p>Given the current dynamics of the epidemic and its uncertain nature, we wished to prolong our inclusion period by 12 months. The number of inclusions per month and per centre will be 1 to 2 patients.</p>

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2703 **Amendment 3 to the Protocol – Version 4.0 of 18/03/2022**

2704

Concerned section and page	Initial text	Modified/added text	Rationale
<p><b>Summary:</b></p> <p><b>Secondary objectives and endpoints</b></p>		<p>Add the following secondary objective and endpoint:</p> <p>4. <i>Net clinical benefit of anticoagulation as assessed by the absence of all-cause death, thrombotic event, MBE, and HIT at Day 28</i></p>	<p>The net clinical benefit of anticoagulation is used to evaluate the efficacy of the treatment (prevention of thrombosis) while taking into account patient's tolerance to treatment (absence of bleeding events or heparin-induced thrombocytopenia). This secondary</p>
<p><b>3.2 Secondary objectives</b></p>		<p>Add the following secondary objective:</p> <p>- <i>Net clinical benefit of</i></p>	

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		<i>anticoagulation as assessed by the absence of all-cause death, thrombotic event, major bleeding event and HIT.</i>	objective is widely used in clinical trials to evaluate anticoagulation strategies <sup>35</sup>
<b>4.2 Secondary endpoints</b>		Add the following secondary endpoint:  4.2.1.4 Net clinical benefit  - <i>Composite of all-cause death, thrombotic event (as defined in paragraph 4.2.1.2), MBE (as defined in paragraph 4.2.1.3), and HIT at day 28</i>	

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