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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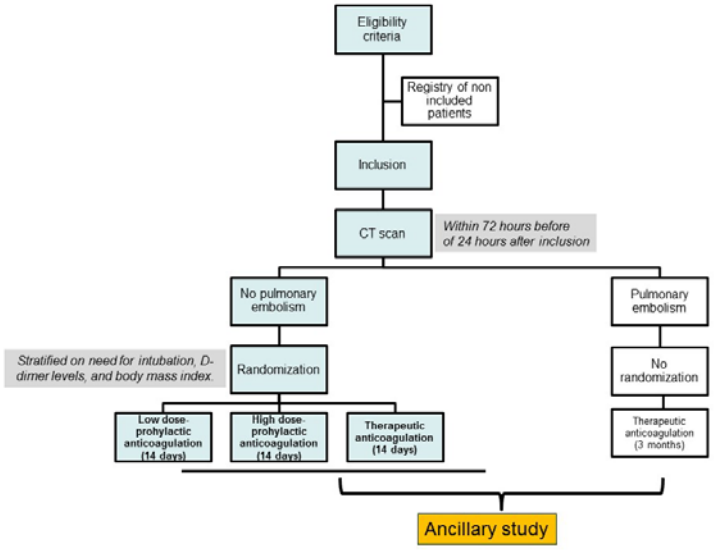
1 SUMMARY

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	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 [1] due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality [2–4]. 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 [2–4]. 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 [4]. 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 [5,6]. 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 [5–7]. No randomized trial has validated this approach, and other recent recommendations challenge this approach [6,8]. 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 [9]. 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 [2,10,11]. 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 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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13]. 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.
Main objective and primary endpoint	The main objective is to compare the efficacy of three strategies (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). 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. 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. 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 [14], as proposed by Coa et al [15], 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. The weaning of ventilation and of supplemental oxygen will be

	protocolized.
Secondary objectives and endpoints	The secondary objectives are to compare the benefit and risks of the three strategies (LD-PA, HD-PA, and TA) regarding: 1. Mortality, morbidity and organ dysfunction; - Score on WHO Ordinal Scale and seven category ordinal scale at Day-28; - Number of days alive and free from supplemental oxygen at Day-28; - Proportion of patients needing intubation at Day-28; - Number of days alive and free from invasive mechanical ventilation at Day-28; - Number of days alive and free from vasopressors at Day-28; - Length of intensive care unit stay; - Length of hospital stay; - Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L); - All-cause deaths at Day-28 and Day-90. 2. Efficacy on thrombotic events - 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; - D-dimers and Sepsis-Induced Coagulopathy Score (SCS) at Day-7. 3. Tolerance of anticoagulation - Proportion of patients with at least one major bleeding event (MBE) at Day-28; - Proportion of patients with at least one life-threatening bleeding event at Day-28; - Proportion of patients with any bleeding event at Day-28 - Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28. 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.
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	1. Age ≥ 18 years; 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 ≥ 5; 3. Written informed consent (patient, next of skin or emergency

	situation). In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion for inclusion.
Exclusion criteria	1. Pregnancy and breast feeding woman; 2. Postpartum (6 weeks); 3. Extreme weights (<40 kg or >100 kg); 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); 5. Need for therapeutic anticoagulation; 6. Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding 7. Platelet count < 50 G/L; 8. Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia; 9. Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis; 10. Severe renal failure (creatinine clearance <30 mL/min); 11. Iodine allergy; 12. Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin; 13. History of type II heparin-induced thrombocytopenia; 14. Chronic oxygen supplementation; 15. Moribund patient or death expected from underlying disease during the current admission; 16. Patient deprived of liberty and persons subject to institutional psychiatric care; 17. Patients under guardianship or curatorship; 18. Participation to another interventional research on anticoagulation.
Interventions or product under investigation	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 the CTPA is positive (pulmonary artery thrombosis), the patient will not be randomized and will receive TA according to the recommendations for thromboembolic disease. - 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).



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^2).

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 unfractioned 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 ≥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 [16,17]. In order to randomize 300 patients, we aim at including 353 patients.
Number of centres	24
Schedule for the study	- Inclusion period: 6 months - Participation period (treatment + follow-up): 90 days - Total duration: 9 months
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.

	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.
Funding sources	Leo Pharma

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2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH

2.1.1 About the condition under investigation

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 [1] due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality [2–4].

The incidence of macrovascular thrombotic event varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of arterial or vein thrombosis captured and severity of illness [2–4]. 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 event [4]. Recently, Suh et al. conducted a large review including 27 observational studies and 3342 patients with COVID-19. The authors report a pulmonary embolism incidence rate of 14.8% (95% CI: 8.5, 24.5; I2 = 0.94) despite prophylactic anticoagulation (PA) (24). 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 event with dose escalation anticoagulation including a high dose-preventive anticoagulation (HD-PA) or a therapeutic anticoagulation (TA) [5–7]. No randomized trial has validated this approach, and other recent recommendations challenge this approach [6,8].

Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even in the absence of obvious macrovascular thrombotic event. A large review of autopsy findings in COVID-19-related death reported micro thrombi in small pulmonary vessels [9]. 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 [2,10,11]. 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 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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13].

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

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

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

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

- A TA is used in one third of patients;

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

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

2.1.3 Current randomized clinical trials

Several trials are studying various doses for anticoagulation strategy in COVID-19 patients [8].

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

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

Firstly, the inclusion criteria differ because of systematic (ANTICOVID) vs. non-systematic (INSPIRATION, COVIDOSE, REMAPCAP, ACTIV-4, ATTACC) investigation of macro-thrombosis, which is de facto an indication for curative anticoagulation. ANTICOVID excludes macrothrombosis from randomization (chest computed tomography with pulmonary angiogram before randomization to exclude pulmonary embolism) and will provide an answer to the specific question of micro thrombosis. Microvascular arterial and venous thrombotic events are a 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 death reported micro thrombi in small pulmonary vessels [9]. More generally, COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs leads to widespread microvascular thrombosis with microangiopathy and occlusion of capillaries [2,10,11], which may ultimately contribute to organ failure. In this respect, the ANTICOVID study is complementary of other studies.

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

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

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

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

Trials	Prophylactic anticoagulation		Weight-based intermediate anticoagulation	Curative anticoagulation
	Lower	Higher		
ANTICOVID, 3 arms	X	X		X
INSPIRATION, 2 bras	X	X[b]	X[a]	
COVIDOSE, 2 arms	X (lower in CW / higher in ICU)		X[b]	
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

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

[a] enoxaparin, 1 mg/kg

[b] adjustment different from that of INSPIRATION; see Table 2

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

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 UIX2/j	70%

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

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.

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.

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).

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.

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).

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).

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).

2.1.4 About comparator strategies/procedures

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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13].

2.2 Hypothesis for the study

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

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.

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

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

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

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 all participating centers 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 unfractioned 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 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.

2.5 Interventions added for the research

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

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

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

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

3 OBJECTIVES OF THE RESEARCH

3.1 Main objective of the research

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

3.2 Secondary objectives

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

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

3.3 Objectives of any ancillary study

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

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

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

The modalities of TA in patients with a positive CTPA will be left at the discretion of the physician in charge of the patient and will follow actual guidelines [20].

4 Description of the research

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

4.1 Primary endpoint

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

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 an ordinal clinical scale derived from a WHO recommended instrument (Table 1 [14]). Clinical improvement will be assessed through a seven-category ordinal scale derived from the WHO scale, as proposed by Coa et al [15], 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 ECMO, invasive mechanical ventilation, or both; and 7. death. As all included patients will at least require oxygen supplementation, live discharge from hospital will represent a minimal 2-points decrease in the 7-points scale, thus a clinical improvement.

Table 1: The WHO ordinal scale [14]

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, PaO2/FIO2 >= 150	7
	Invasive ventilation PaO2/FIO2 <150 or catecholamine	8
	Requiring ECMO or dialysis	9
Death	Death	10

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

4.2 Secondary endpoints

4.2.1.1 Efficacy on morbi-mortality and organ function

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

4.2.1.2 Efficacy on thrombotic events

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

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

4.2.1.3 Tolerance of anticoagulation

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

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

- Proportion of patients with at least one life-threatening bleeding event at Day-28. The bleeding event is life-threatening if it meets at least one of the following criteria according to the RE-LY definitions [24]: fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in hemoglobin of ≥50 g/L, or bleeding requiring transfusion of ≥ 4 units of blood; necessitating surgical, endoscopic, or endovascular action.
- Proportion of patients with at any bleeding event at Day-28 of randomization including major and minor bleeding events. Minor bleeding events will be defined as all non-major bleeding events.
- Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28

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

5 Description of research methodology

5.1 Design of the study

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

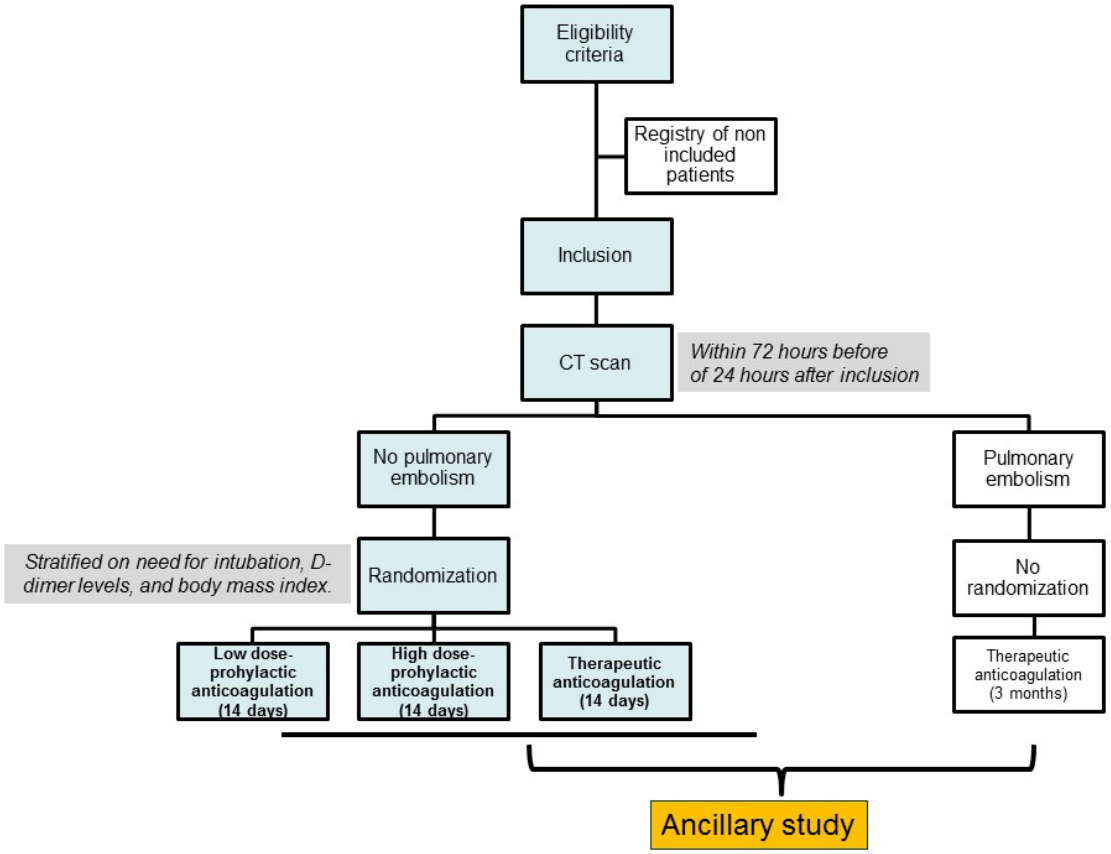

Figure 1: Experimental schema.

Definition of abbreviations: CTPA, computed tomography pulmonary arteries.

5.2 Number of participating sites

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

5.3 Description of measures taken to reduce and prevent biases

5.3.1 Identification of participants

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

5.3.2 Randomisation

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

A randomization number will be assigned when the participant is randomized. This number will have the following format: RXXXX. Centralized blocked randomization according to a 1:1:1 ratio will be prepared by the Clinical Research Unit (URC-MONDOR) before the start of the trial. It will be carried out in balanced blocks and stratified by hospital center and according to the following criteria at inclusion: 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^2).

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

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

6 Implementation of the study

6.1 Schedule for the study

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**
- 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)	Case 1: the patient is informed at the inclusion visit if he/she is able to express his/her will Case 2: 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 Case 3: 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	Case 1: the patient gives his/her consent at the inclusion visit Case 2: 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 Case 3: 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

A multidetector CTPA (chest computed tomography with pulmonary angiogram) will be performed within 72 hours before or 24 hours after inclusion. The CTPA modalities will be standardized across the different centers, according to the following recommendations [25]. The injection will consist of 100 to 120 ml of low osmolality non-ionic contrast product with a high iodine concentration (300 to 400 mg/mL iodine concentration; example: Iomeron 400®, BYC laboratories, Paris, France) using an automatic injector, with a flow rate of 3 to 5 ml/sec [25]. Helical acquisition will be done in standard filter, 64 x 0.625 mm, from the 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. The analysis of the pulmonary arteries up to the sub-segmental level will be performed by the radiologists in charge of patients, according to usual practice and standards. A thrombus will be taken into account in case of intraluminal defect of the contrast material or in case of total occlusion of the vessel by low density material.

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

- If the CTPA is positive (elastic artery thrombosis), the patient will not be randomized and will receive TA according to the recommendations for thromboembolic disease.
- 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).

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

6.1.3 Follow-up visits

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

6.1.3.1 Day-7 visit

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

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

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

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

- Heparin induced thrombocytopenia.

6.1.4 Last study visit

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

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

If the patient is discharged from the hospital:

- the CRT will collect the medical records from the clinical departments where the patient stayed in the period; these will be analyzed by the investigator who included the patient;
- the CRT will collect data on the vital status and occurrence of serious adverse events of the patient:
  - (if necessary) telephone contact with the patient (3 different attempts, days and times over 15 days);
  - (if necessary) telephone contact with the physician in charge of the patient during the period;
  - (if necessary) telephone contact with the patient's treating or referring physician(s);
  - (if necessary) contact of the town council of the patient birthplace.

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

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

Actions (C= care; R= research)	**Day-1 (inclusion)**	**Day-1 (randomization)**		**Day-2 to Day-14**	***(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		

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

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

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

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

7.2 Exclusion criteria

- Pregnancy and breast feeding woman;
- Postpartum (6 weeks);
- Extreme weights (<40 kg or >100 kg);
- 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);
- Need for therapeutic anticoagulation;
- Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding
- Platelet count < 50 G/L;
- Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;
- Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;
- Severe renal failure (creatinine clearance <30 mL/min);
- Iodine allergy;
- Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;
- History of type II heparin-induced thrombocytopenia;
- Chronic oxygen supplementation;
- Moribund patient or death expected from underlying disease during the current admission;
- Patient deprived of liberty and persons subject to institutional psychiatric care;
- Patients under guardianship or curatorship;
- Participation to another interventional research on anticoagulation.

7.3 Recruitment procedure

	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
Number of participants/center/month	**2 to 3**

8 TERMINATION rules

Several situations are possible

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

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

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

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

- The case report form must list the various reasons why the participant has discontinued the study:
  - ☐ Adverse reaction
  - ☐ Another medical issue
  - ☐ Personal reasons of the participant
  - ☐ Explicit withdrawal of consent.

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

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

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

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

8.1.1 **Management of a bleeding event**

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

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

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

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

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

8.1.3 Full or partial discontinuation of the study

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

9 EFFICACY ASSESSMENT

9.1 Description of efficacy assessment parameters

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

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

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

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

Actions (C= care; R= research)	**Day-0** (inclusion)	**Day-1** (randomization)		**Day-2 to Day-14**	**Day-1 to Day-28** *(or hospital discharge)*	**Day-90** *+/- 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

10 VIGILANCE

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

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

10.1 Definitions

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

- **Adverse event**

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

- **Adverse reaction**

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

- **Serious adverse event or reaction**

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

- **Unexpected adverse reaction**

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

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

- **Emerging safety issue**

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

For example, this concerns:

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

10.2 The role of the investigator

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

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

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

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

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

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

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

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

Table: WHO-UMC : causality categories

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

**Or study procedures

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

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.2.2 Specific features of the protocol

- Adverse events deemed “medically significant”

- Thrombotic and bleeding events

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

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

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

10.3 Role of the adjudication committee

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

The adjudication committee assesses:

- thrombotic and bleeding events
- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific strategy tested by the study,
  All serious adverse events which the investigator and/or the adjudication committee believe could have a causal relationship with the strategy tested

- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the strategies tested.

Serious adverse events likely to be related to the strategies tested :
- major bleeding events
- life threatening bleeding events

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

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

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

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

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

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

11 Specific study committees

11.1 Steering committee

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

Members:

- principal investigator (Dr Vincent LABBE),

- scientific supervisor (Pr Armand MEKONTSO DESSAP),

- biostatistician (Pr Etienne AUDUREAU),

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

Role:

- Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
- Propose procedures to be followed during the study, acknowledging any recommendations from the Steering Committee.

11.2 Adjudication committee

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

Members:

- Pr Nadia AISSAOUI
- Dr Mathieu SCHMIDT

Role:

- Review and adjudicate reported thrombotic and bleeding events, as well as deaths and serious adverse events
- The committee will meet after every 60 inclusions in the study.

12 data management

12.1 Data collection procedures

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

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

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

12.3 Right to access data and source documents

12.3.1 Data access

In accordance with GCPs:

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

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

12.3.2 Source documents

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

12.3.3 Data confidentiality

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

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

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

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

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

12.4 Data processing and storage of research documents and data

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

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

12.4.2 Data entry

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

12.5 Data ownership

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

13 statistical aspects

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

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

Descriptive analyses

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

Primary endpoint analysis

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 clinical improvement. 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 a non-parametrical Mann-Whitney test.

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

Secondary endpoints

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13.4 Anticipated level of statistical significance

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

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

13.5 Statistical criteria for termination of the study

Not applicable.

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

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

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

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

13.8 Selection of populations

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

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

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

14 QUALITY CONTROL AND ASSURANCE

14.1 General organisation

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

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

14.1.1 Strategy for opening the centres

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

14.1.2 Data quality control

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

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

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

14.2 Case report forms

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

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

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

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

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

14.3 Management of non-compliances

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

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

14.4 Audit

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

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

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

14.5 Principal Investigator's commitment to assume responsibility

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

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

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

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

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

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

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

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

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

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

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

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

In practice, the consent will be obtained as follows:

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

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

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

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

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

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

15.3 Compensation for participants

15.3.1 Reimbursement of expenses **incurred**

Not applicable.

15.3.2 Compensation

There will be no compensation.

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

Not applicable.

15.5 Legal obligations

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

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

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

15.7 Informing the ANSM

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

15.8 Procedures relating to data protection regulations

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

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

15.9 Amendments to the research

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

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

15.10 Final study report

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

15.11 Archiving

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

This indexed archiving includes, in particular:

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

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

16 Funding and Insurance

16.1 Funding sources

LEO Pharma

16.2 Insurance

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

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

17 Publication rules

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

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

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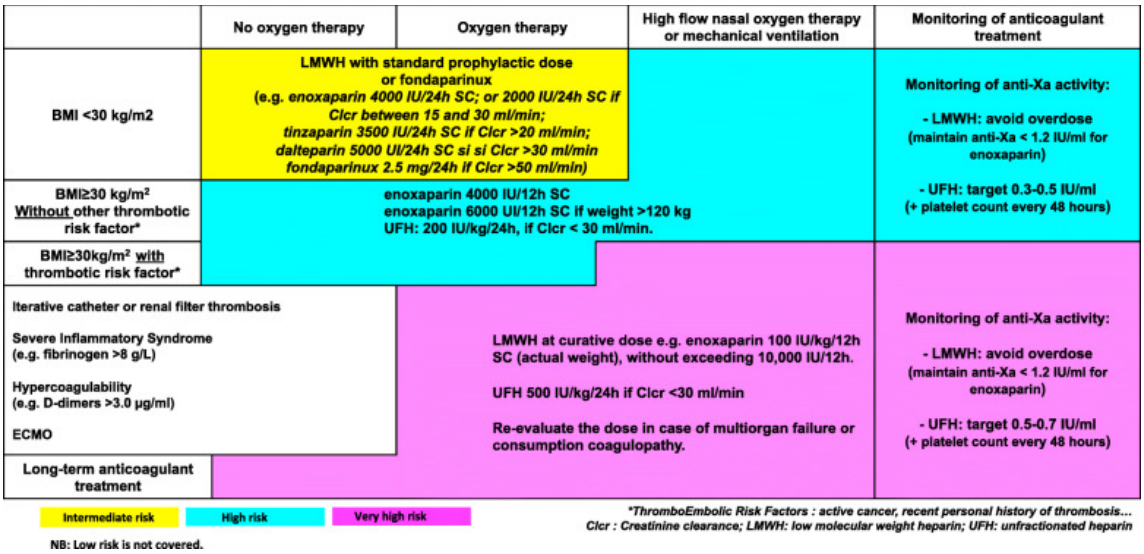
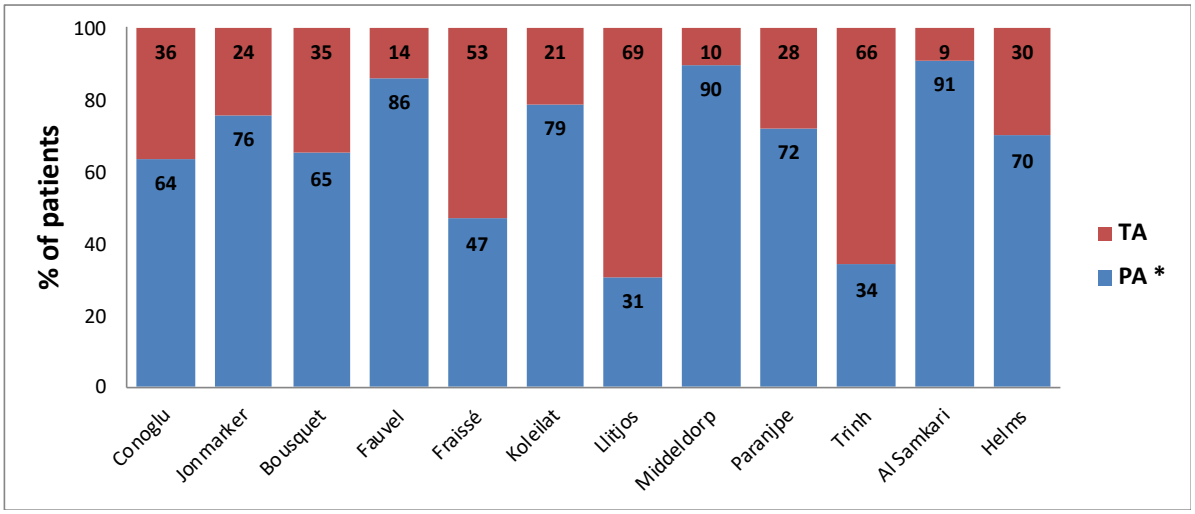
19 List of addenda

19.1 Annex 1: Prevention and treatment of thrombosis in hospitalized patients with COVID-19 [7]



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



Abbreviations: TA, therapeutic anticoagulation ; PA, preventive anticoagulation

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

Reference: [4,12,13,27–33]

19.3 Annex 3: sepsis-induced Coagulopathy Score [34]

Variable		Points
INR	≤1.2	0
	>1.2 to 1.4	1
	>1.4	2
Platelet count, cells x 10^9/L	≥150	0
	100 to <150	1
	<100	2
Total SOFA score*	0	0
	1	1
	≥2	2

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

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

Variable	Response (Please select the one sentence that best describes your health today ?)
MOBILITY	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
SELF-CARE	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
USUAL ACTIVITIES *(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
PAIN / DISCOMFORT	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
ANXIETY / DEPRESSION	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
HEALTH TODAY	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.

19.5 Annex 5: Definition of thrombotic events and bleeding events

Variable	Définition
Thrombotic event	
Ischemic stroke [21]	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 [21]
Deep venous thrombosis (DVT)	Confirmed by venous duplex compression ultrasonography or CT-scan [22]
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
Bleeding event	
Major bleeding event (ISTH definition, [23])	Meets ≥1 of the following criteria: - symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardia, or intramuscular with compartment syndrome; - bleeding associated with a reduction in hemoglobin of ≥2 g/dl (1.24 mmol/l) or leading to transfusion of ≥2 U blood or packed cells ; - fatal bleeding.
Life-threatening bleeding event (RE-LY definition [24])	Meets ≥1 of the following criteria: - fatal bleeding; - symptomatic intracranial bleeding; - bleeding with a decrease in hemoglobin of ≥50 g/L, or bleeding requiring transfusion of ≥ 4 units of blood; necessitating surgical, endoscopic, or endovascular action;
Intracranial bleeding (ISTH Definition, [23])	Intracerebral bleedings, subdural bleedings, epidural bleedings or subarachnoid bleedings.
Fatal bleeding (ISTH Definition, [23])	Bleeding event that is the primary cause of death or contributes directly to death.

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

19.6 Annex 6 : List of Investigators

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3 Final version of Protocol

Research code number: APHP201624

Title: "ANTIcoagulation in severe COVID-19 patients: a multicenter, parallel-group, open-label, randomized controlled trial"

ANTICOVID

Version no. 4.0

dated: 18 / 03 / 2022

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

Coordinating Investigator:

Dr Vincent LABBE — Date: ……/……/……..

Department: Intensive Care Unit — Signature:

Hospital: Tenon, AP-HP

4 rue de la Chine

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Sponsor

Assistance Publique – Hôpitaux de Paris — Date: ……/……/……..

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75010 PARIS

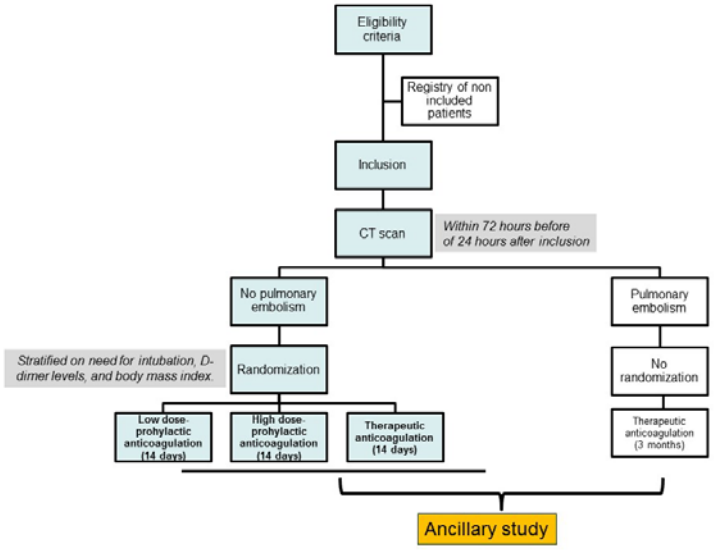
1 SUMMARY

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	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 [1] due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality [2–4]. 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 [2–4]. 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 [4]. 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 [5,6]. 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 [5–7]. No randomized trial has validated this approach, and other recent recommendations challenge this approach [6,8]. 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 [9]. 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 [2,10,11]. 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

	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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13]. 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.
Main objective and primary endpoint	The main objective is to compare the efficacy of three strategies (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). 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. 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. 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 [14], as proposed by Coa et al [15], 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. The weaning of ventilation and of supplemental oxygen will be protocolized.
Secondary objectives	The secondary objectives are to compare the benefit and risks of the three

and endpoints	strategies (LD-PA, HD-PA, and TA) regarding: 4. Mortality, morbidity and organ dysfunction; - Score on WHO Ordinal Scale and seven category ordinal scale at Day-28; - Number of days alive and free from supplemental oxygen at Day-28; - Proportion of patients needing intubation at Day-28; - Number of days alive and free from invasive mechanical ventilation at Day-28; - Number of days alive and free from vasopressors at Day-28; - Length of intensive care unit stay; - Length of hospital stay; - Quality of life at Day-90 assessed using a quality of life questionnaire (EQ5D5L); - All-cause deaths at Day-28 and Day-90. 5. Efficacy on thrombotic events - 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; - D-dimers and Sepsis-Induced Coagulopathy Score (SCS) at Day-7. 6. Tolerance of anticoagulation - Proportion of patients with at least one major bleeding event (MBE) at Day-28; - Proportion of patients with at least one life-threatening bleeding event at Day-28; - Proportion of patients with any bleeding event at Day-28 - Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28. 7. Net clinical benefit of anticoagulation as assessed by the absence of all-cause death, thrombotic event, MBE, and HIT at Day-28. 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.
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	1. Age ≥ 18 years; 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 ≥ 5;

	3. Written informed consent (patient, next of skin or emergency situation). In view of the exceptional and urgent situation, affiliation to a social security scheme will not be a criterion for inclusion.
Exclusion criteria	19. Pregnancy and breast feeding woman; 20. Postpartum (6 weeks); 21. Extreme weights (<40 kg or >100 kg); 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); 23. Need for therapeutic anticoagulation (except for COVID-related pulmonary thrombosis); 24. Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding 25. Platelet count < 50 G/L; 26. Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia; 27. Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis; 28. Severe renal failure (creatinine clearance <30 mL/min); 29. Iodine allergy; 30. Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin; 31. History of type II heparin-induced thrombocytopenia; 32. Chronic oxygen supplementation; 33. Moribund patient or death expected from underlying disease during the current admission; 34. Patient deprived of liberty and persons subject to institutional psychiatric care; 35. Patients under guardianship or curatorship; 36. Participation to another interventional research on anticoagulation.
Interventions or product under investigation	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. - 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. - 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).



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^2).

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 unfractioned 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 ≥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 [16,17]. In order to randomize 300 patients, we aim at including 353 patients.
Number of centres	26 recruiting hospitals in France.
Schedule for the study	- Inclusion period: 18 months - Participation period (treatment + follow-up): 90 days - Total duration: 21 months
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.

	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.
Funding sources	Leo Pharma

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2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH

2.1.1 About the condition under investigation

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 [1] due to a state of profound inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality [2–4].

The incidence of macrovascular thrombotic event varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of arterial or vein thrombosis captured and severity of illness [2–4]. 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 event [4]. Recently, Suh et al. conducted a large review including 27 observational studies and 3342 patients with COVID-19. The authors report a pulmonary embolism incidence rate of 14.8% (95% CI: 8.5, 24.5; I2 = 0.94) despite prophylactic anticoagulation (PA) (24). 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 event with dose escalation anticoagulation including a high dose-preventive anticoagulation (HD-PA) or a therapeutic anticoagulation (TA) [5–7]. No randomized trial has validated this approach, and other recent recommendations challenge this approach [6,8].

Microvascular thrombotic events are also of major concern in critically ill patients with COVID-19, even in the absence of obvious macrovascular thrombotic event. A large review of autopsy findings in COVID-19-related death reported micro thrombi in small pulmonary vessels [9]. 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 [2,10,11]. 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 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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13].

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

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

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

prospective investigations. Moreover, they acknowledged the difficulty to evaluate the specific thrombotic risk for each patient, even with the use of D-dimers, whose thresholds are not consensual [8].

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

- A TA is used in one third of patients;

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

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

2.1.3 Current randomized clinical trials

Several trials are studying various doses for anticoagulation strategy in COVID-19 patients [8].

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

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

Firstly, the inclusion criteria differ because of systematic (ANTICOVID) vs. non-systematic (INSPIRATION, COVIDOSE, REMAPCAP, ACTIV-4, ATTACC) investigation of macro-thrombosis, which is de facto an indication for curative anticoagulation. ANTICOVID excludes macrothrombosis from randomization (chest computed tomography with pulmonary angiogram before randomization to exclude pulmonary embolism) and will provide an answer to the specific question of micro thrombosis. Microvascular arterial and venous thrombotic events are a 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 death reported micro thrombi in small pulmonary vessels [9]. More generally, COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs leads to widespread microvascular thrombosis with microangiopathy and occlusion of capillaries [2,10,11], which may ultimately contribute to organ failure. In this respect, the ANTICOVID study is complementary of other studies.

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

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

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

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

Trials	Prophylactic anticoagulation		Weight-based intermediate anticoagulation	Curative anticoagulation
	Lower	Higher		
ANTICOVID, 3 arms	X	X		X
INSPIRATION, 2 bras	X	X[b]	X[a]	
COVIDOSE, 2 arms	X (lower in CW / higher in ICU)		X[b]	
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

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

[a] enoxaparin, 1 mg/kg

[b] adjustment different from that of INSPIRATION; see Table 2

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

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 UIX2/j	70%

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

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.

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.

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).

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.

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).

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).

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).

2.1.4 About comparator strategies/procedures

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<0.001) [12]. Similar findings were recently reported by Jonmarker et al [13].

2.2 Hypothesis for the study

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

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.

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

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

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

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 all participating centers 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 unfractioned 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 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.

2.5 Interventions added for the research

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

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

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

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

3 OBJECTIVES OF THE RESEARCH

3.1 Main objective of the research

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

3.2 Secondary objectives

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

- Morbi-mortality and organ function;

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

3.3 Objectives of any ancillary study

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

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

The modalities of TA in patients with a positive CTPA will be left at the discretion of the physician in charge of the patient and will follow actual guidelines [20].

4 Description of the research

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

4.1 Primary endpoint

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

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 an ordinal clinical scale derived from a WHO recommended instrument (Table 1 [14]). Clinical improvement will be assessed through a seven-category ordinal scale derived from the WHO scale, as proposed by Coa et al [15], 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 ECMO, invasive mechanical ventilation, or both; and 7. death. As all included patients will at least require oxygen supplementation, live discharge from hospital will represent a minimal 2-points decrease in the 7-points scale, thus a clinical improvement.

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, PaO2/FIO2 >= 150	7
	Invasive ventilation PaO2/FIO2 <150 or catecholamine	8
	Requiring ECMO or dialysis	9
Death	Death	10

Table 1: The WHO ordinal scale [14]

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

4.2 Secondary endpoints

4.2.1.1 Efficacy on morbi-mortality and organ function

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

4.2.1.2 Efficacy on thrombotic events

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

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

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

4.2.1.3 Tolerance of anticoagulation

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

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

4.2.1.4 Net clinical benefit

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

5 Description of research methodology

5.1 Design of the study

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

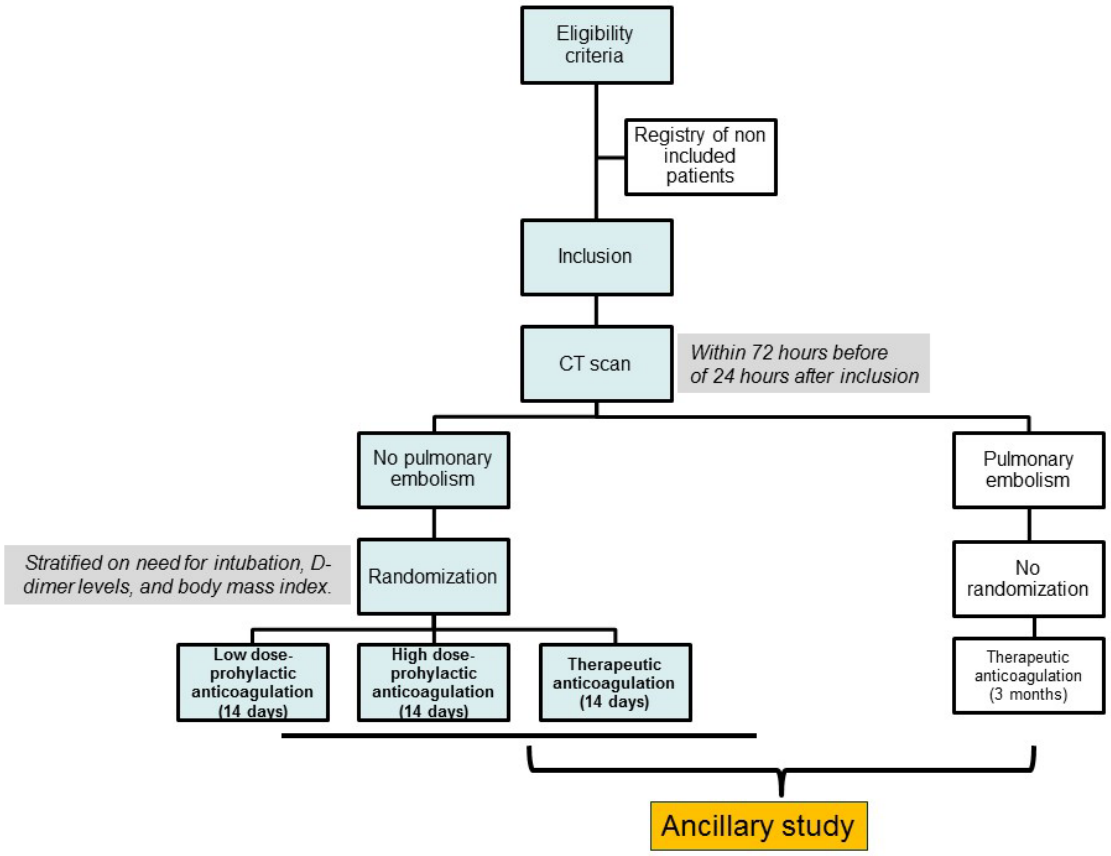

Figure 1: Experimental schema.

Definition of abbreviations: CTPA, computed tomography pulmonary arteries.

5.2 Number of participating sites

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

5.3 Description of measures taken to reduce and prevent biases

5.3.1 Identification of participants

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

5.3.2 Randomisation

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

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

A randomization number will be assigned when the participant is randomized. This number will have the following format: RXXXX. Centralized blocked randomization according to a 1:1:1 ratio will be prepared by the Clinical Research Unit (URC-MONDOR) before the start of the trial. It will be carried out in balanced blocks and stratified by hospital center and according to the following criteria at inclusion: 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^2).

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

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

6 Implementation of the study

6.1 Schedule for the study

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

6.1.1 Screening visit

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

6.1.2 Inclusion visit

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

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

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)	Case 1: the patient is informed at the inclusion visit if he/she is able to express his/her will Case 2: 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 Case 3: 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	Case 1: the patient gives his/her consent at the inclusion visit Case 2: 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 Case 3: 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

A multidetector 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. The CTPA modalities will be standardized across the different centers, according to the following recommendations [25]. The injection will consist of 100 to 120 ml of low osmolality non-ionic contrast product with a high iodine concentration (300 to 400 mg/mL iodine concentration; example: Iomeron 400®, BYC laboratories, Paris, France) using an automatic injector, with a flow rate of 3 to 5 ml/sec [25]. Helical acquisition will be done in standard filter, 64 x 0.625 mm, from the 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. The analysis of the pulmonary arteries up to the sub-segmental level will be performed by the radiologists in charge of patients, according to usual practice and standards. A thrombus will be taken into account in case of intraluminal defect of the contrast material or in case of total occlusion of the vessel by low density material.

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

- If the CTPA is positive (elastic artery thrombosis), the patient will not be randomized and will receive TA according to the recommendations for thromboembolic disease.
- 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).

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

6.1.3 Follow-up visits

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

6.1.3.1 Day-7 visit

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

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

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

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

6.1.4 Last study visit

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

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

If the patient is discharged from the hospital:

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

- (if necessary) telephone contact with the patient's treating or referring physician(s);
- (if necessary) contact of the town council of the patient birthplace.

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

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

Actions (C= care; R= research)	**. (inclusion)**	**(randomizati on)**		**Day-2 to Day-14**	**Day-28 *(or hospital*	***+/- 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		
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.						

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

- Age ≥ 18 years ;

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

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

7.2 Exclusion criteria

- Pregnancy and breast feeding woman;
- Postpartum (6 weeks);
- Extreme weights (<40 kg or >100 kg);
- 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);
- Need for therapeutic anticoagulation (except for COVID-related pulmonary thrombosis);
- Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding
- Platelet count < 50 G/L;
- Within 15 days of recent surgery, within 24 hours of spinal or epidural anesthesia;
- Any prior intracranial hemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;
- Severe renal failure (creatinine clearance <30 mL/min);
- Iodine allergy;
- Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;
- History of type II heparin-induced thrombocytopenia;
- Chronic oxygen supplementation;
- Moribund patient or death expected from underlying disease during the current admission;
- Patient deprived of liberty and persons subject to institutional psychiatric care;
- Patients under guardianship or curatorship;
- Participation to another interventional research on anticoagulation.

7.3 Recruitment procedure

It is a national multicenter study.

Recruitment of patients will be conducted in various departments of selected hospital centers but also in various “COVID” units that will be created according to the organization of each hospital. Theses departments and units will be unified in a « COVID center » in each hospital.

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
Number of participants/center/month	**1**

8 TERMINATION rules

Several situations are possible

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

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

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

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

- The case report form must list the various reasons why the participant has discontinued the study:
  - ☐ Adverse reaction
  - ☐ Another medical issue
  - ☐ Personal reasons of the participant
  - ☐ Explicit withdrawal of consent.

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

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

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

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

8.1.1 Management of a bleeding event

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

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

8.1.2 Management of heparin-induced thrombocytopenia (HIT)

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

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

8.1.3 Full or partial discontinuation of the study

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

9 EFFICACY ASSESSMENT

9.1 Description of efficacy assessment parameters

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

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

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

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

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

Actions (C= care; R= research)	**Day-1 (inclusion)**	**Day-1 (randomization)**		**Day-2 to Day-14**	***(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

10 VIGILANCE

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

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

10.1 Definitions

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

- **Adverse event**

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

- **Adverse reaction**

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

- **Serious adverse event or reaction**

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

- **Unexpected adverse reaction**

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

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

- **Emerging safety issue**

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

For example, this concerns:

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

10.2 The role of the investigator

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

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

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

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

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

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

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

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

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

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

**Or study procedures

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

A serious adverse event is any untoward medical occurrence that:

6- results in death
7- is life-threatening to the participant enrolled in the study
8- requires hospitalisation or prolongation of existing hospitalisation
9- results in persistent or significant disability/incapacity
10- is a congenital anomaly/birth defect

10.2.2 **Specific features of the protocol**

- Adverse events deemed “medically significant”
  - Thrombotic and bleeding events

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

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

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

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

10.3 Role of the adjudication committee

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

The adjudication committee assesses:

- thrombotic and bleeding events
- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific strategy tested by the study,
  All serious adverse events which the investigator and/or the adjudication committee believe could have a causal relationship with the strategy tested

- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the strategies tested.

Serious adverse events likely to be related to the strategies tested :
- major bleeding events
- life threatening bleeding events

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

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

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

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

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

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

11 Specific study committees

11.1 Steering committee

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

Members:

- principal investigator (Dr Vincent LABBE),

- scientific supervisor (Pr Armand MEKONTSO DESSAP),

- biostatistician (Pr Etienne AUDUREAU),

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

Role:

- Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
- Propose procedures to be followed during the study, acknowledging any recommendations from the Steering Committee.

11.2 Adjudication committee

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

Members:

- Pr Nadia AISSAOUI
- Dr Mathieu SCHMIDT

Role:

- Review and adjudicate reported thrombotic and bleeding events, as well as deaths and serious adverse events
- The committee will meet after every 60 inclusions in the study.

12 data management

12.1 Data collection procedures

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

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

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

12.3 Right to access data and source documents

12.3.1 Data access

In accordance with GCPs:

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

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

12.3.2 Source documents

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

12.3.3 Data confidentiality

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

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

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

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

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

12.4 Data processing and storage of research documents and data

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

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

12.4.2 Data entry

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

12.5 Data ownership

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

13 statistical aspects

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

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

Descriptive analyses

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

Primary endpoint analysis

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 clinical improvement. 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 a non-parametrical Mann-Whitney test.

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

Secondary endpoints

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13.4 Anticipated level of statistical significance

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

13.5 Statistical criteria for termination of the study

Not applicable.

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

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

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

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

13.8 Selection of populations

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

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

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

14 QUALITY CONTROL AND ASSURANCE

14.1 General organisation

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

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

14.1.1 Strategy for opening the centres

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

14.1.2 Data quality control

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

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

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

14.2 Case report forms

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

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

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

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

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

14.3 Management of non-compliances

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

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

14.4 Audit

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

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

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

14.5 Principal Investigator's commitment to assume responsibility

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

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

The Principal Investigator at each participating center will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative. In this study, a Principal Investigator will be declared for each COVID center, grouping multiple participating department and COVID units within a hospital in accordance with the specific care of COVID patients as well as organizational changes related to the scale of the pandemic.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

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

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

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

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

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

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

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

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

In practice, the consent will be obtained as follows:

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

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

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

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

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

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

15.3 Compensation for participants

15.3.1 Reimbursement of expenses **incurred**

Not applicable.

15.3.2 Compensation

There will be no compensation.

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

Not applicable.

15.5 Legal obligations

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

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

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

15.7 Informing the ANSM

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

15.8 Procedures relating to data protection regulations

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

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

15.9 Amendments to the research

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

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

15.10 Final study report

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

15.11 Archiving

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

This indexed archiving includes, in particular:

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

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

16 Funding and Insurance

16.1 Funding sources

LEO Pharma

16.2 Insurance

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

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

17 Publication rules

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

This study has been registered on the website http://clinicaltrials.gov/ under number 04808882.

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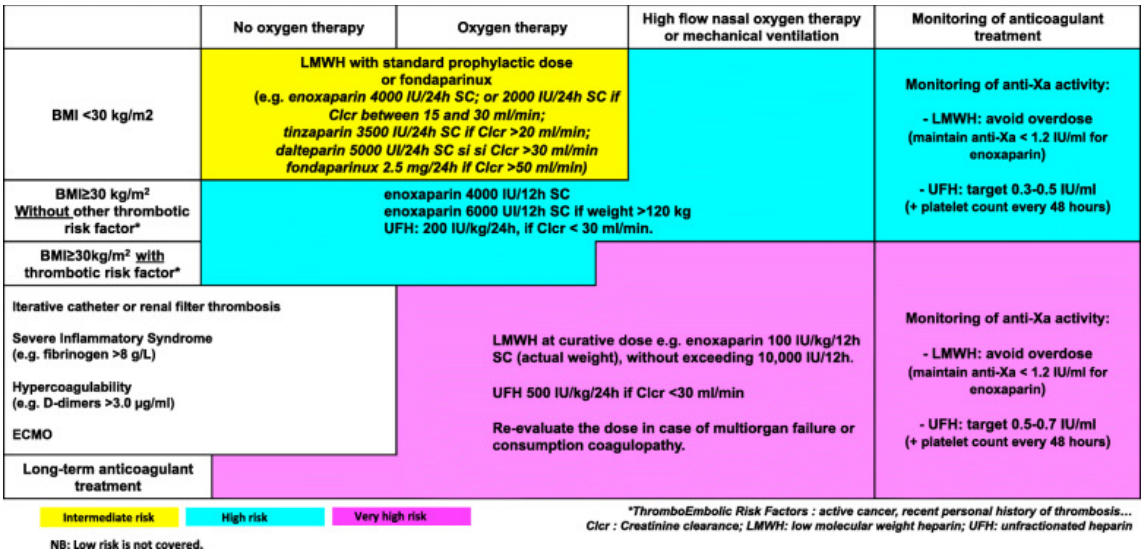
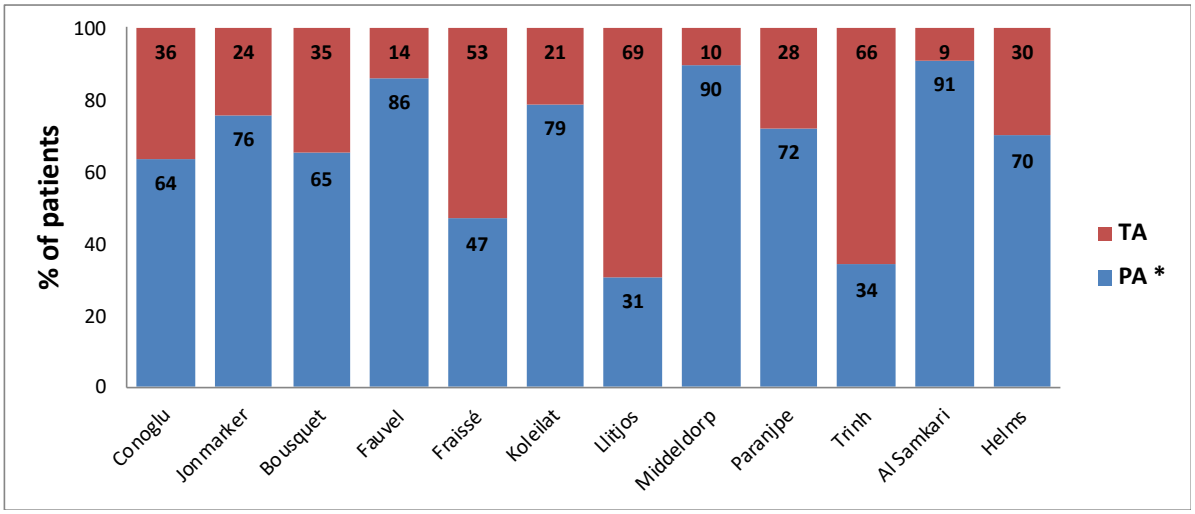
19 List of addenda

19.1 Annex 1: Prevention and treatment of thrombosis in hospitalized patients with COVID-19 [7]



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



Abbreviations: TA, therapeutic anticoagulation ; PA, preventive anticoagulation

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

Reference: [4,12,13,27–33]

19.3 Annex 3: sepsis-induced Coagulopathy Score [34]

Variable		Points
INR	≤1.2	0
	>1.2 to 1.4	1
	>1.4	2
Platelet count, cells x 10^9/L	≥150	0
	100 to <150	1
	<100	2
Total SOFA score*	0	0
	1	1
	≥2	2

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

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

Variable	Response (Please select the one sentence that best describes your health today ?)
MOBILITY	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
SELF-CARE	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
USUAL ACTIVITIES *(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
PAIN / DISCOMFORT	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
ANXIETY / DEPRESSION	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
HEALTH TODAY	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.

19.5 Annex 5: Definition of thrombotic events and bleeding events

Variable	Définition
Thrombotic event	
Ischemic stroke [21]	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 [21]
Deep venous thrombosis (DVT)	Confirmed by venous duplex compression ultrasonography or CT-scan [22]
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
Bleeding event	
Major bleeding event (ISTH definition, [23])	Meets ≥1 of the following criteria: - symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardia, or intramuscular with compartment syndrome; - bleeding associated with a reduction in hemoglobin of ≥2 g/dl (1.24 mmol/l) or leading to transfusion of ≥2 U blood or packed cells ; - fatal bleeding.
Life-threatening bleeding event (RE-LY definition [24])	Meets ≥1 of the following criteria: - fatal bleeding; - symptomatic intracranial bleeding; - bleeding with a decrease in hemoglobin of ≥50 g/L, or bleeding requiring transfusion of ≥ 4 units of blood; necessitating surgical, endoscopic, or endovascular action;
Intracranial bleeding (ISTH Definition, [23])	Intracerebral bleedings, subdural bleedings, epidural bleedings or subarachnoid bleedings.
Fatal bleeding (ISTH Definition, [23])	Bleeding event that is the primary cause of death or contributes directly to death.

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

19.6 Annex 6: List of Investigators

Nom	Prénom	Courriel	Etablissement(s) de santé	Site d'exercice, GH	Ville	Pays	Centre COVID
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							COVID
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PREAU	Sebastien	Sebastien.PREAU@CHRU-LILLE.FR	CHU Lilles	CHU Lilles	Lilles	France	Médecine Intensive Réanimation et autres unités du centre COVID
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4 Protocol summary of changes

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

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

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

Concerned section	Initial text	Modified/added text	Rationale
Summary: Exclusion criteria 7.2 Exclusion criteria	Need for therapeutic anticoagulation	Need for therapeutic anticoagulation *(except for COVID-related pulmonary thrombosis);*	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).
Summary: Interventions or product under investigation 6.1.2 Inclusion visit 6.2 Table or diagram summarising the chronology of the study, with distinction between standard	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. *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.*	Clarification on CTPA. 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. This strategy aims to

care and research			spare patients unnecessary re-exposure to radiation and contrast agents.
Summary: Interventions or product under investigation 2.4 Interventions and products which will be performed or used as standard	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.	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. *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.*	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
Summary Number of centres 5.2 Number of participating sites 7.3 Recruitment procedure Annex 6: List of investigators	24 This is a multicentre research in which 24 university-affiliated hospitals would like to participate. Number of centres: 24 Number of participants/centre:15	*26 recruiting hospitals in France.* This is a multicentre research in which *26* university-affiliated hospitals would like to participate. Number of centres: *26* Number of participants/centre: 13 to 14 *Dr William JUGUET* *william.juguet@aphp.fr*	Given the dynamics of the epidemic, we aimed to increase our recruitment potential to 26 centres

		CH Avicenne – Jean Verdier AP-HP, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Bondy France *Réanimation et autres unités du centre COVID* *CH Louis-Mourier AP-HP. Nord - Université de Paris, Colombes France* *Médecine Intensive Réanimation et autres unités du centre COVID*	
7.3 Recruitment procedure		*It is a national multicentre study.* *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. Theses departments and units will be unified in a single "COVID centre" in each hospital.* *In each hospital, assigned investigators are likely to recruit and follow patients in that "COVID centre".*	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
14.5 Principal Investigator's commitment to undertake responsibility	**[…]** 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. The investigators and their staff will sign a	**[…]** 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. *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*	

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

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

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

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

Concerned section and page	Initial text	Modified/added text	Rationale
Summary: Secondary objectives and endpoints		Add the following secondary objective and endpoint: *4. Net clinical benefit of anticoagulation as assessed by the absence of all-cause death, thrombotic event, MBE, and HIT at Day 28*	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
3.2 Secondary objectives		Add the following secondary objective: - *Net clinical benefit of*	

		anticoagulation as assessed by the absence of all-cause death, thrombotic event, major bleeding event and HIT.	objective is widely used in clinical trials to evaluate anticoagulation strategies [35]
4.2 Secondary endpoints		Add the following secondary endpoint: 4.2.1.4 Net clinical benefit - *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*	

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