

**Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: comparison of 40 mg o.d.
versus 40 mg b.i.d. A randomized Clinical Trial**

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: comparison of 40 mg o.d. versus 40 mg b.i.d. A randomized Clinical Trial
Internal ref. no. (or short title)	X-Covid 19
Promoter	ASST Grande Ospedale Metropolitano Niguarda
Principal Investigator	Marco Cattaneo / Nuccia Morici
EudraCT Number	2020-001708-41
Clinical Phase	Phase IIIb
Trial Design	Open-label Multicentre Prospective Controlled Randomized Trial in patients with SARS-CoV-2 infection. Patients will be randomized 1:1 to 40 mg subcutaneous enoxaparin o.d. versus 40 mg enoxaparin b.i.d within 12 hours after hospitalization.
Trial Participants Inclusion criteria	<ul style="list-style-type: none"> All-comers patients aged ≥ 18 years and admitted to hospital with laboratory-confirmed SARS-CoV-2 infection.
Exclusion criteria	<ul style="list-style-type: none"> Patients admitted directly to an intensive care unit; Estimated creatinine clearance < 15 ml/min/1.73m²; Patients needing anticoagulant for prior indication; Participants involved in other clinical trials; Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
Planned Sample Size	A sample of 2712 subjects is required to test the superiority hypothesis with 80% power according to a two-sided 0.05 level of significance that 40 mg enoxaparin b.i.d. will decrease the primary endpoint compared to 40 mg enoxaparin o.d. An event rate of 10% was hypothesized in the control arm and 7% in the treatment arm, corresponding to a 33% relative risk reduction.
Treatment duration	In-hospital (at least 30 days of therapy)
Follow up duration	30 days from the enrolment
Planned Trial Period	6 months
Primary Objective	To compare the effects of 40 mg subcutaneous enoxaparin o.d. versus 40 mg enoxaparin b.i.d on the incidence of venous thromboembolism (VTE) [a composite of incident asymptomatic and symptomatic deep vein thrombosis (DVT) diagnosed by serial compression ultrasonography (CUS), and symptomatic pulmonary embolism (PE) diagnosed by CT scan], in patients with SARS-CoV-2 infection.

<p>Secondary Objectives</p>	<ul style="list-style-type: none"> • To compare the effects of 40 mg subcutaneous enoxaparin o.d. versus 40 mg enoxaparin b.i.d on the incidence of in-hospital major complications, defined as the composite of death, VTE, use of mechanical ventilation, stroke, acute myocardial infarction and admission to an intensive care in patients with SARS-CoV-2. • To compare each single component of the primary endpoint between the two groups. • To compare maximum sequential organ failure assessment (SOFA) score between the two groups. • To compare C-reactive protein, D-dimer, IL-6 and hs-troponin levels (as % above the upper reference limit [URL]) among the two groups. • To compare the incidence of SARS-CoV-2-related Acute Respiratory Distress Syndrome (ARDS) between the two groups. • To compare length of hospital stay between the two groups. • To compare measures of right ventricular function at trans-thoracic echocardiography or CT between admission and follow-up, whenever available.
<p>Safety Endpoints</p>	<ul style="list-style-type: none"> • To compare the incidence of bleeding events according to the <i>ISTH bleeding scale</i> between the two groups. • To compare the incidence of bleeding events according to <i>BARC classification</i> between the two groups. Only BARC 3 and 5 will be considered for secondary endpoint. • To assess the incidence of heparin-induced thrombocytopenia in the two groups.

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BARC	Bleeding Academic Research Consortium
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

4. BACKGROUND AND RATIONALE

Critically ill medical patients are at heightened risk for venous thromboembolism (VTE) and, for this reason, they are treated with prophylactic doses of low molecular weight heparin (LMWH) (for instance, 40 mg enoxaparin). Patients with COVID-19, which is caused by SARS-CoV-2 infection, are apparently at particularly high risk of VTE, as a consequence of excessive activation of the hemostatic system which, in the most severe cases, could also be associated with the formation of microthrombi and clinically relevant disseminated intravascular coagulation.¹⁻⁴

Based on personal communications by medical doctors working mostly in Northern Italy, there are concerns about the efficacy of thromboprophylaxis with low-molecular-weight heparin (LMWH) at the standard doses in these patients, given their apparently very high risk of thromboembolic complications. Therefore, in many Northern Italian hospitals these patients are given LMWH at much higher doses than those recommended for thromboprophylaxis: in some hospitals, full anticoagulant doses (100 U/Kg b.i.d.) are being used even in the absence of evidence of ongoing thromboembolic disease. This practice does not take into due account the obvious risk of major, potentially fatal bleeding that is associated with high dosing, in the absence of any evidence of higher efficacy of high doses compared to standard prophylactic doses.

An additional rationale for the use of high dose LMWH in many hospitals is that hyper-activation of the hemostatic system in COVID-19 patients could lead to the formation of microthrombi in pulmonary vessels⁵, causing further respiratory distress, and in vessels of other vital organs, causing multi-organ failure (MOF). However, there is no demonstration that this therapeutic approach decreases the risk of microangiopathic thrombosis in these patients, as well as, for that matter, in other types of patients.

Given this scenario, we designed a randomized trial comparing standard prophylactic dose of subcutaneous enoxaparin (40 mg o.d.) with higher dose (40 mg b.i.d) with the aim of testing whether high-dose thromboprophylaxis is more effective than standard dose in preventing TEV in COVID-19 patients. This study would also allow us to test whether double-dose prophylaxis with enoxaparin would favourably affect the natural history of the disease, by decreasing the incidence of organ dysfunction associated with the formation of microthrombi in vital organs.

Patients will be monitored every 3 days with D-dimer, fibrinogen, complete blood count, lactate dehydrogenase (LDH), PT, APTT, C-reactive protein, procalcitonin only in the case of superinfection by a different agent, ferritin, creatine phosphokinase (CK), CK-MB, albumin, serum creatinine, aspartate transaminase (AST), alanine transaminase (ALT), high-sensitivity troponin, serum bilirubin and interleukine-6 along with other examinations according to clinical practice.

Patients will be monitored every seven days from the enrolment with CUS of the lower limbs for proximal DVT screening. For patients who display signs and symptoms of DVT, CUS will be performed as soon as possible in the same day. Proximal DVT, namely DVT of iliac, femoral and popliteal veins down to popliteal trifurcation, is defined by cross-sectional vein incompressibility or direct thrombus imaging with vein enlargement. Distal DVT might be reported if distal segments are explored.

For patients who display signs and symptoms of pulmonary embolism, a CT scan will be performed as soon as possible in the same day according to the indication of the attending physician. Multidetector CT pulmonary angiography is the method of choice for imaging the pulmonary vasculature in patients with suspected pulmonary embolism, that is defined by contrast-filling defects.

With regard to secondary objective, the following definitions apply.

All-cause mortality includes all deaths, regardless of whether the cause of death is determined. Cardiovascular death is defined as death due to atherosclerotic coronary heart disease, cerebrovascular accident or (complication of) peripheral embolization, and includes deaths due to acute MI, stroke, sudden death, non-sudden death, unwitnessed death, and procedure-related deaths. Non-cardiovascular death includes deaths due to all other causes.

Myocardial Infarction denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers [Cardiac troponin I (cTnI) and T (cTnT) increased above the 99th percentile upper reference limit (URL)] in the setting of evidence of acute myocardial ischaemia.

Stroke is defined as any new neurological deficit lasting >24 hours. CT or MRI are required to confirm the stroke and to distinguish between ischemic and hemorrhagic stroke. Strokes will be also classified as fatal or nonfatal: nonfatal stroke will be also classified as disabling and non disabling.

The total duration of the study is 6 months for enrolment, follow-up, data collection, cleaning and analysis.

7. PARTICIPANT IDENTIFICATION

7.1 Trial participants

Patients directly admitted to hospital for suspected SARS-CoV-2 infection will be screened for randomization.

7.2 Inclusion Criteria

All the following inclusion criteria will be adopted:

All-comers patients aged ≥ 18 years and admitted to hospital with laboratory-confirmed SARS-CoV-2 infection.

7.3 Exclusion Criteria

The following patients will not be enrolled:

- Patients admitted directly to intensive care unit.
- Patients with estimated creatinine clearance < 15 ml/min/1.73m².
- Patients needing anticoagulant for prior indication.
- Participants involved in other clinical trial.
- Patients with any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

8 TRIAL PROCEDURES

Eligibility will be evaluated by the attending physician after the first visit and after confirmation of the diagnosis. The patient, properly informed about the study, will be able to decide to sign the informed consent and the privacy form. The physician will obtain a detailed anamnesis and he/she will carefully check the clinical parameters needed to define tissue perfusion (as detailed by the inclusion criteria) along with body temperature. The following laboratory data will be checked: haemochrome, renal function, serum electrolytes, liver function, coagulation, blood gas analysis. Laboratory examinations will be sequentially evaluated according to the flow chart timeline (section 8.6). If the patient develops a condition needing an anticoagulation, an increase in enoxaparin dosage to 100 UI/kg (1 mg/kg) b.i.d. might be considered if indicated and in the absence of contraindications. Serial CUS will be performed, the first on admission and then every seven days. Bleeding events will be registered and graded according to the International Society on Thrombosis and Haemostasis (ISTH) bleeding scale and Bleeding Academic Research Consortium (BARC) scale. Also BARC 2 bleedings will be recorded.

Pre-specified subgroup analyses will be performed for 1) D-dimer categories (>1 <2 , 2, 3, 4, 5, 6 fold the ULN of the reference range); 2) estimated creatinine clearance ($<$ versus >60 ml/min/1.73 m²); 3) severity

of the respiratory symptoms (mild versus moderate-severe defined as respiratory rate ≥ 30 breaths/min; arterial oxygen saturation $\leq 93\%$ at rest; $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg); 4) concomitant antiplatelet therapy.

The identification of adverse reactions will be continuous during hospitalisation. The data will be recorded in an eCRF.

8.1 Recruitment

Patients recruitment will be performed at the Cardiology Department, Malattie Infettive and Internal Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; Medicina, Ospedale San Paolo, ASST Santi Paolo e Carlo, Milan, Italy; Istituto Clinico Città Studi, Milan, Italy; IRCCS Policlinico San Donato, Milan, Italy; AOU Città della Salute e della Scienza, Presidio Molinette, Torino, Italy; Ospedale Sacco, Milan, Italy; IRCCS Policlinico San Matteo, Pavia, Italy; ASST Monza – Ospedale di Monza, Monza, Italy; AOU Ospedali Riuniti di Ancona, Ancona, Italy; ASST Spedali Civili di Brescia, Brescia, Italy; Ospedale Andrea Gallino, ASL 3 Genovese, Genova, Italy; IRCCS Istituto Clinico Humanitas, Rozzano, Milan, Italy; ASST Lecco, Ospedale A. Manzoni, Lecco, Italy.

8.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished, taking into consideration the urgency of treatments, to consider the information and the opportunity to ask the Investigator, his/her GP or other independent parties to decide whether he/she will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and authorized to do so by the Chief/Principal Investigator. The original signed Informed Consent will be given to the participant and a copy will be retained at the trial site.

8.3 Screening and Eligibility Assessment

As clinically indicated, the screening procedures will be performed throughout demographics, medical history, concomitant medication, physical examination, laboratory tests and radiological findings (chest CT scans are encouraged over chest X-rays).

The screening procedure will be immediately followed by recruitment at arrival in the ward (patients will not be randomized in the emergency department), if allowed on basal evaluation and patient informed consent signature.

8.4 Randomisation, blinding and code-breaking

This study will be a two-parallel group randomized, open-label, multi-center trial in hospitalized COVID-19 patients. Patients will be randomized by the attending physicians using an IVRS that randomizes at a ratio of 1:1 upon determination of eligibility.

A total sample of 2712 subjects is required to test the superiority hypothesis with 80% power according to a two-sided 0.5 level of significance that 40 mg enoxaparin subcutaneously bid/day (treatment arm) will decrease the primary endpoint compared to 40 mg enoxaparin/day (prophylaxis dose, that is considered the control arm as represents the standard of care for hospitalized patients that are bedridden). An absolute reduction of 3% is foreseen in the treatment arm (enoxaparin 40 mg b.i.d); an event rate of 10% was considered in the control arm (enoxaparin 40 mg o.d.) and 7% in the treatment arm.

The duration of the enrolment is 3 months from the obtaining of the approvals. The total duration of the study is 6 months for follow-up (1 months), data collection, cleaning and analysis (2 months). Randomisation will be done at the same visit as the baseline visit. There will not be a run-in period.

8.5 Baseline Assessments

Basal evaluation (V1)

Every patient will be informed about the objectives of our study and he/she will be asked for consent to the trial. At basal visit and following ones, the physician will perform: physical examination, hemodynamic parameters and blood gas analysis check; CUS. Echocardiogram might be performed if requested by the attending physician.

The occurrence of organ dysfunction and failure, from admission through days spent in intensive care, will be assessed by the Sequential Organ Failure Assessment (SOFA) score.

8.6 Subsequent Visits

After basal assessment, the following visits will be performed according to local clinical practice a check-up at discharge will be performed. Echocardiograms might be performed during hospitalization according to the indication of the attending physician. In case mechanical ventilation is required, ventilation modes and eventual variations of parameters will be recorded.

The schedule of clinical visits and assessment procedures is shown in the following flow chart.

Flow chart

Visit	V1	V2	V2	V3	V4
Time interval	Basal	To be checked each three days	To be checked each seven days	Discharge	30-day from the enrolment
Informed consent	X				
Time from onset symptoms to enrolment	X				
Physical examination	X				
Height	X				
Weight	X				
Anamnesis	X				X
BP (s/d/m)	X				
HR	X	X		X	
CUS	X		X		
Hb	X	X		X	
Creatinine	X	X		X	
Platelets	X	X		X	
Leucocytes	X	X		X	
INR	X	X		X	
Bilirubin	X	X		X	
AST	X	X		X	
ALT	X	X		X	
LDH	X	X		X	
CRP	X	X		X	
Troponin (HS)	X	X		X	
IL-6	X	X		X	
D-dimer	X	X		X	
Fibrinogen	X	X		X	
SOFA score	X	X			

8.7 Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of trial treatment or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of trial treatment or results in inability to continue to comply with trial procedures
- Withdrawal of Consent

Withdrawal from the trial will result in exclusion of the data for that participant from analysis

The reason for withdrawal will be recorded in the eCRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.8 Definition of End of Trial

The end of trial is the date of the last visit/ telephone follow up/ home visit of the last participant.

9. COMPLIANCE WITH TRIAL TREATMENT

All patients will be treated in hospital ward, so compliance will be guaranteed by the investigators.

10. ACCOUNTABILITY OF TRIAL TREATMENT

The study does will involve drugs usually administrated in clinical practice.

11. CONCOMITANT MEDICATION

There are not any contraindicated medications. All used drugs, as per clinical indication, will be reported in the eCRF.

12. POST-TRIAL TREATMENT

At the end of the study period, all surviving patients will be treated as per current clinical practice in the participating Centers.

13. SAFETY REPORTING

13.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product or diagnostic-interventional procedure has been administered, including occurrences which are not necessarily caused by or related to that product or procedure.
Adverse Reaction (AR)	<p>An untoward and unintended response in a participant to a medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect. <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p>

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

13.2. Causality

The relationship of each adverse event to trial treatment must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial treatment start. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

13.3. Procedures for Recording Adverse Events

All AEs occurring during the trial / or until the following two months that are observed by the Investigator or reported by the participant, will be recorded on the eCRF, whether or not attributed to trial treatment.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial treatment, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs considered related to the trial treatment as judged by a medically qualified investigator will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether an AE is of enough severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

13.4. Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the SAE reporting form to Eudravigilance within 24 hours of the Site Study Team becoming aware of the event.

Review of SAEs must be timely, taking into account the reporting time for a potential SUSAR.

13.5. Expectedness

Expectedness will be determined according to the Investigators' Brochure/Summary of Product Characteristics.

13.6. SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the investigator team is first aware of the reaction. Any additional information will be reported within 15 calendar days. Treatment codes will be un-blinded for specific participants.

13.7. Safety Monitoring Committee

The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

14. STATISTICS

14.1. Description of Statistical Methods

All protocol-defined endpoints will be measured from the time of randomization. Descriptive statistics of baseline characteristics of patients randomized to the two groups will be reported. Continuous variables will be summarized by means, standard deviations, medians, inter-quartile ranges and minimum and maximum values. Categorical variables will be summarized by frequencies and percentages.

Data will be analysed according to the intention-to-treat principle. In addition, a per-protocol analysis of the primary endpoint, considering patients without major protocol violations (i.e. patients who crossed over), will be performed to evaluate the robustness of the data.

A test for difference of proportions will be carried out to compare in-hospital composite events among patients randomized to the two groups. A relative risk will be calculated to quantify the magnitude of the half anticoagulant effect.

For what regards continuous secondary endpoints, maximum SOFA score will be compared among the study groups through the t-test or Wilcoxon rank-sum test, according to the distribution of study endpoints.

The same approach will be applied for laboratory examinations and times included in the secondary endpoints.

All tests will be two-sided and a p-value of 0.05 or less will be considered statistically significant. No adjustments for multiple testing will be applied in the analysis of secondary endpoints and in the subgroup analysis, therefore, inferences drawn from the reported p-values and 95% CIs will be considered exploratory. If a p-value is less than 0.001 it will be reported as “<0.001”.

14.2. Number of Participants

Summary Statements

The proportion for the primary endpoint is estimated to be 0.07 in the half-dose anticoagulant dose and 0.10 in the standard group. With a type I error α set to 0.05 and a power $1 - \beta$ set to 0.8, a total of 2712 subjects will be enrolled in the trial.

14.3. Populations Analysis

For this trial, the following populations will be defined and used in the analysis and/or presentation of the data.

Safety population: The safety population will be classified according to the actual treatment on enoxaparin 40 mg b.i.d. or control, received.

Intent-to-treat (ITT) population: Treatment classification for ITT analysis will be based on the randomized treatment.

Per-Protocol (PP) population: The PP population will be defined as all ITT patients who received assigned to enoxaparin 40 mg b.i.d. and will be without major protocol violations. Specifically, subjects may be excluded from PP population if any of the following criteria are met:

- Inclusion/Exclusion criteria violations;

The PP definition for each patient will be finalized before database lock and study unblinding.

The primary and secondary efficacy analyses will be based on the ITT population. Analyses based on the PP population will be considered supportive.

14.4. Criteria for the Termination of the Trial

Criteria refers to the above reported statistical plan (section 14.2).

14.5. Procedure for Accounting for Missing, Unused, and Spurious Data

All data will be checked for consistency and plausibility based on the nature of each collected variable before any statistical analysis. Data falling beyond limits of plausibility will be checked in the medical records and in the CRF to correct for possible typos or transcription errors. Changes in the database will be recorded together with date and name of the physician performing that correction and with the reason for correction.

Methods of multiple imputation will be considered if the missingness rate will be more than 20%.

14.6. Inclusion in Analysis

All patients will be included in the analysis

14.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

All the statistical analysis procedures, all the possible deviations, and all the reporting operations will be performed according to the Statistical Principles for Clinical Trials (E9, ICH Harmonised Tripartite Guideline).

The statistical report will contain the log of any of the operation conducted on the database, plus, possible comments (preceded by a “%” symbol) if and when needed. Any deviation from the original statistical plan will be therefore reported in the log, together with the reason behind the deviation.

15. DATA MANAGEMENT

15.1. Source Data

Source documents are the first recorded data and from which participants’ eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

15.2. Access to Data

Direct access will be granted to authorised representatives from promoter and the regulatory authorities to permit trial-related monitoring, audits and inspections.

15.3. Data Recording and Record Keeping

All trial data will be entered on an electronic CRFs.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

16. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance to the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

17. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Promoter becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Promoter must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

18.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

18.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) and regulatory authorities for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC. In addition, an End of Trial notification and final report will be submitted to the REC.

18.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant ID number on the eCRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

18.6. Expenses and Benefits

They will not be intended payments to participants and any other benefits.

18.7. Other Ethical Considerations

Nothing to declare

19. FINANCE AND INSURANCE

19.1. Funding

None.

19.2. Insurance

The study compares two accepted treatment modalities of patients with COVID-19. As per DM 17.12.2004, art 2, comma 4, patients will be covered by hospital insurance.

ASST Grande Ospedale Metropolitano will guarantee for patients' insurance.

20. PUBLICATION POLICY

The final manuscript of the study will be prepared by the Principal Investigators.

The data will remain property of the Promoters.

21. REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020.
2. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol*. 2020 Mar 4.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020 Feb 19.
4. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, Brown TS, Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Cardiol*. 2020 Mar 18. pii: S0735-1097(20)34637-4.
5. Luo W, Yu H, Gou J, et al. Clinical Pathology of Critical Patient with Novel Coronavirus Pneumonia (COVID-19). *Preprints*. 2020, 2020020407.
6. Darzi AJ, Karam SG, Charide R, Etzeandía Ikobaltzeta I, Cushman M, Gould MK, Mbuagbaw L, Spencer F, Spyropoulos A, Streiff MB, Woller SC, Zakai N, Germini F, Rigoni M, Agarwal A, Morsi RZ, Iorio A, Akl E, Schunemann HJ. Prognostic factors for VTE and Bleeding in Hospitalized Medical Patients: a systematic review and meta-analysis. *Blood*. 2020 Feb 24. pii: blood.2019003603.
7. Mehran R, Rao SV, Bhatt DL, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. A Consensus Report from the Bleeding Academic Research Consortium. *Circulation*. 2011; 123:2736-2747.