Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial

A pragmatic randomized open-label study of the safety and efficacy of the combination of Colchicine and Rosuvastatin in addition to standard of care (SOC) compared to SOC alone in hospitalized patients with SARS-CoV-2

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Study Phase 4

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1.0 Document Control

1.1 Version History

Version	Description
1.0 23 June 2020	Initial Release
2.0 8 February 2021	- Changed Primary Endpoint to include thromboembolic complications. - Allowed for use of SpO2 when PaO2 not available to calculate SOFA score for secondary endpoints - Changed inclusion criteria to allow for enrollment within 72 hours of admission. - Changed exclusion criteria to allow for enrollment of non ICU patients requiring BiPAP/CPAP or HFNC (WHO ordinal scale 5) - Changed exclusion criteria to allow for enrollment of patients on chronic oral corticosteroid therapy - Changed exclusion criteria to allow for patients with WBC ≥ 2,500 to be enrolled - Updated trial timeline - Clarified recommended lab work

1.2 Protocol Approval Page

Study title: **Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial**

A pragmatic randomized open-label study of the safety and efficacy of the combination of colchicine and rosuvastatin in addition of standard of care (SOC) compared to SOC alone in hospitalized patients with SARS-CoV-2

Protocol version: 2.0

Protocol date: 8 February 2021

Alexandra Lansky, MD Principal Investigator Yale Cardiovascular Research Group	Date
Michael Cleman, MD Co-Investigator Yale School of Medicine	Date
Charles Dela Cruz, MD Co-Investigator Yale School of Medicine	Date
Gil Lancaster, MD Sub-Investigator Bridgeport Hospital	Date
Chris Howes, MD Sub-Investigator Greenwich Hospital	Date
Brian Cambi, MD Sub-Investigator Lawrence & Memorial Hospital	Date

1.3 Investigator Signature Page

Study title: **Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial**

A pragmatic randomized open-label study of the safety and efficacy of the combination of colchicine and rosuvastatin compared to standard of care (SOC) in hospitalized patients with SARS-CoV-2

Protocol version: 2.0

Protocol date: 8 February 2021

Investigator's Responsibility

Prior to participation in the Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial, as the site principal investigator, I understand that I must obtain written approval from my Institutional Review Board. This approval must include my name and a copy must be provided to the Yale University (or designee), along with the approved Patient Information and Consent Form prior to the first enrollment at my study site.

As the site Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, applicable laws, any conditions of approval imposed by the Yale Institutional Review Board, local regulations where applicable, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki, and ensure that all study personnel are appropriately trained prior to any study activities.
2. Ensure that the study is not commenced until all approvals have been obtained.
3. Ensure that written informed consent is obtained from each subject prior to any data collection, using the most recent Institutional Review Board approved Patient Information and Consent Form.
4. Provide all required data and reports and agree to source document verification of study data with patient's medical records by Yale University (or designee) and any regulatory authorities.
5. Allow Yale University personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws.

Investigator Signature

I have read and understand the contents of the Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial protocol and agree to abide by the requirements set forth in this document.

_____	_____
Investigator Name (print)	Investigative Site (print)
_____	_____
Investigator Signature	Date

2.0 Protocol Synopsis

Title:	**Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial**
Investigational Drug	**Colchicine** is an extensively studied oral anti-inflammatory agent with a well-defined safety profile. Colchicine, by inhibiting tubulin polymerization and clathrin-mediated endocytosis has the potential to inhibit SARS-CoV-2 cell entry. In addition, colchicine has a direct anti-inflammatory effect by inhibiting the NLRP3 inflammasome activation which in turn has the potential to reduce the SARS-CoV-2-induced cytokine storm. **Statins** also have direct anti-inflammatory effects by reducing chemokine release, adhesion molecules, and modulating T cell activity and have the potential to prevent SARS-CoV-2 related endothelial dysfunction and may reduce the morbidity and mortality associated with COVID-19. Rosuvastatin, in particular, appears to have direct antiviral properties by binding and inhibiting the active site of the main protease enzyme (M^{pro}) of SARS-CoV-2. The combination ***Colchicine* + Rosuvastatin** may have a synergetic effect to antagonize SARS-CoV-2 infection, modulate the inflammatory response and to reduce morbidity and mortality associated with acute respiratory distress syndrome (ARDS) and myocardial injury in COVID-19 patients. Both drugs have been in use for decades for gout and pericarditis (colchicine) and hyperlipidemia, coronary disease (CAD) and diabetes (rosuvastatin/Crestor), and have been tested in thousands of patients used individually and in combination with a low and well characterized risk profile. Colchicine and rosuvastatin are currently used as standard of care in COVID-19 patients whether due to pre-existing CAD, gout or pericarditis or acute presentations with acute coronary syndromes or acute gout with no expected added risk in the population being studied. This study is not intended to support a labeling change or advertising claim for either drug, and the study will be conducted in compliance with the requirements of Yale University's IRB review and a research IND.
Objective	To investigate the safety and efficacy of the combination of ***Colchicine*** + **Rosuvastatin** added to standard of care (SOC) compared to SOC alone in hospitalized subjects with moderate COVID-19.
Study Type	This is a prospective 1:1 randomized open-label clinical trial
Study Design	Subjects will be screened within 48 hours of hospital admission. Patients with real-time reverse transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection and meeting all inclusion and exclusion criteria, will be randomized to either ***Colchicine*** + **Rosuvastatin** treatment in addition to SOC or SOC alone for the duration of hospitalization. Subjects will be randomized in a 1:1 manner to one of two arms: **<u>Active treatment</u>:** In addition to SOC* subjects randomized to active treatment will receive:

	• ***Rosuvastatin: 40mg daily AND*** • ***Colchicine: 0.6mg twice daily for 3 days then 0.6mg daily*** **Note:** Dose adjustment based on medical conditions and drug interactions (see section §7.4.1). Subjects previously on chronic statin therapy will be eligible for enrollment in the trial, and if randomized to active treatment, chronic statin therapy will be discontinued and replaced by rosuvastatin 40 mg for 30 days or hospital discharge and resumed thereafter. **Standard of Care Controls:** Subjects will undergo SOC treatment determined by the primary care team and the YNHH treatment algorithm for hospitalized patients with COVID-19. *All standard of care treatments for hospitalized subjects with SARS-CoV-2 are permitted concurrently with the study intervention. This only includes treatments approved by the Yale SOC treatment Committee. Concomitant therapy will be performed according to standard practice, local standards of care and published guidelines. Subjects will not be permitted to participate in other investigational studies. Methods for identifying drug interactions and dose adjustment are listed in section §7.4.1 of the protocol. Drug discontinuation is only permitted with documented adverse reactions (section §7.4.3).
Duration of Treatment	Treatment will continue for a total of 30 days. If the subject is discharged the treatment will stop at that time.
Treatment Discontinuation Criteria	Study drug may be discontinued in a subject after review of all available data with the medical monitor and discussion with the investigator if any of the following occur: • Any SAE or ≥ Grade 3 AE is suspected to be related to treatment • Any elevation of ALT>5xULN confirmed by repeat testing • Any elevation of CK >5xULN confirmed by repeat testing • Severe myalgias suspected related to statin therapy • Subjects who develop renal or hepatic impairment and require a protease inhibitor or strong CYP3A4 inhibitor should discontinue colchicine • Subjects who develop new blood dyscrasia including leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia should discontinue colchicine
Sites and Geography	**United States:** Yale New Haven Health System includes Yale New Haven Hospital, St Raphael Campus, Bridgeport Hospital, Greenwich Hospital, and Lawrence and Memorial Hospital in Connecticut

Primary Efficacy Endpoint	**30 day composite of the following:** **1) Progression of COVID-19 disease as defined by the World Health Organization (WHO) Ordinal Scale for Clinical Improvement Scores 5-8 (or 6-8 if patient at score of 5 at time of randomization)*.** **2) Arterial or Venous thromboembolic complications confirmed by imaging (including DVT/PE, MI, and ischemic stroke).** *WHO ordinal scale: • *Score 5*: Hospitalized requiring non-invasive ventilation or high-flow oxygen/high-flow nasal cannula • *Score 6*: Hospitalized requiring intubation and mechanical ventilation • *Score 7*: Hospitalized requiring ventilation and additional organ support (vasopressors, renal replacement therapy, ECMO) • *Score 8*: Death
Primary Safety Endpoint	**Proportion of subjects with treatment emergent adverse events (TEAE)** defined as undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.
Powered Secondary Efficacy Endpoint	**Secondary Powered Efficacy Endpoint assessed at 30 days** defined as a composite of a. **Respiratory failure** requiring invasive mechanical ventilation, b. **Any Myocardial injury** (troponin URL> 99th percentile or a $\geq$2-fold increase if troponin is abnormal at baseline, or a new >10% reduction in LVEF by Echocardiography) c. **Death**
Secondary Endpoints	**Secondary endpoints** will be reported by treatment group at 30 and 60 days: **Clinical Safety and Efficacy:** a. Death (all cause and cardiovascular) b. Duration of oxygen therapy (days) c. Duration of invasive mechanical ventilation (days) d. Duration of intensive care treatment (days) e. Duration of hospitalization (days) f. Any myocardial injury (troponin URL > 99th percentile or a $\geq$2-fold increase if troponin is abnormal at baseline or a new >10% reduction in LVEF by Echocardiography), and underlying ischemic (Fourth Universal definitions) or inflammatory cause g. Venous thrombosis or thromboembolic complication confirmed by imaging h. All stroke (NeuroARC defined) i. Acute kidney injury (AKIN criteria)

	j. Time (in days) to symptomatic improvement: reduction in baseline WHO ordinal score by >2 points or achievement of scores 1-3 k. Overall WHO ordinal scale for clinical improvement at 30 and 60 days **Other Secondary Biomarker Endpoints:** a. Sequential Organ Failure Assessment (SOFA) score, defined by 6 variables (the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems) scored from 0 (normal) to 4 (high degree of dysfunction/failure). b. Change of the SOFA from baseline. c. Peak and change from baseline in routine biomarkers (CRP, procalcitonin, D-dimer, PTT/INR, ferritin, troponin/CK-MB, BNP, CPK, AST, ALT, ALP, bilirubin, white blood cell count), as available. d. Peak and change from baseline in cytokine panel (IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available *If an arterial blood gas (ABG) is not available to calculate the PaO2/FiO2 ratio for the SOFA assessment the SpO2/FiO2 ratio may be used as an alternative per prior literature.[2] **Secondary Imaging Endpoints (Imaging substudy)** a. Proportion of subjects with reduction in LVEF defined as a decrease of more than 10% in LVEF by clinically driven point of care echocardiography measured in hospital b. Cardiac MRI in a subset of subjects with adjudicated suspected myocarditis assessed at 60 days.
Patient Population	A total of 466 adult subjects with RT-PCR confirmed SARS-CoV-2 infection hospitalized with initially moderate (non ICU) COVID-19 will be recruited within 72 hours of admission.
Subject Follow-Up	All subjects will be assessed daily while hospitalized for clinical, biomarker, safety, and laboratory parameters based on the YNHH SOC algorithm. Baseline biomarker measurements and subsequent frequency will be based on each center's SOC but preferably should occur every 24 hours during hospitalization and preferably should include at minimum a basic metabolic panel, CBC with differential, LFTs, CRP, procalcitonin, D-dimer, and troponin (or CK-MB if not available). Cytokine measurement and other labs/imaging will occur according to the SOC of each center. Study treatment will be continued for 30 days or until hospital discharge whichever occurs sooner. All subjects will be followed clinically in hospital, at 30 days and 60 days from trial enrollment. After discharge, the follow-up will be by phone.
Study Committees	**Clinical Events Committee**

	An independent Clinical Events Committee (CEC) will adjudicate all primary and major secondary clinical events potentially meeting endpoint criteria in an ongoing fashion during the trial. **Data and Safety Monitoring Board** An independent Data and Safety Monitoring Board (DSMB) will be responsible for the oversight and safety monitoring of the study. The DSMB will advise the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.
Inclusion Criteria	Subjects must meet **ALL** of the following criteria to be eligible for inclusion in the study: 1. 18 years or older and confirmed SARS-CoV-2 infection by RT-PCR 2. Patient is admitted to the floor or step down (non-ICU) within 72 hours of hospital admission 3. The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions and has provided witnessed (by 2 independent members of the health care team) oral informed consent, or a photograph of the signed informed consent approved by the Institutional Review Board (IRB)
Exclusion Criteria	Subjects will be excluded if **ANY** of the following criteria apply: 1. Known pregnancy or nursing mothers 2. Known allergy to statins or colchicine 3. Patient is on chronic colchicine 4. Acute liver disease defined by elevated transaminases (AST/ALT > 3x ULN) 5. Severe chronic kidney disease defined as glomerular filtration rate (GFR) < 30mL/min1.73 m^2 6. Severe QTc prolongation (>500ms narrow QRS<120ms and >550ms for wide QRS≥120) 7. Presents with severe disease on admission requiring ICU admission (WHO ordinal scale of clinical improvement scores 6-8) 8. Rhabdomyolysis or CPK > 5x ULN 9. Thrombocytopenia defined as platelet count < 50,000 / mm^3 10. Leukopenia defined as white blood cell count < 2,500/ μl 11. Severe anemia defined as Hemoglobin value <8 g/100ml 12. Participation in any other clinical trial of an experimental treatment for COVID-19
Randomization	Randomization will occur using the incorporated EPIC algorithm
Blinding	This is an open-label study. The Clinical Event Committee will be blinded to treatment allocation.
Analysis Plan	***Primary Efficacy Endpoint Analysis:*** The primary efficacy endpoint analysis will be a test of superiority of ***Colchicine + Rosuvastatin*** in addition to SOC compared to SOC alone assessed by the primary outcome of progression to severe COVID-19

	disease (as defined by WHO ordinal scale scores 5-8 or 6-8 if patient at score of 5 at time of randomization) and arterial and venous thromboembolic complications at 30 days. A total of 466 evaluable subjects (233 per group) will provide at least 80% power to test the primary hypothesis assuming a 44% event rate at 30 days in the control group, a 30% relative reduction in events with treatment, a 2-sided α=0.05 and at most 10% loss to follow-up at 30 days. The primary endpoint will be evaluated in the ITT population (defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received). A secondary analysis will be performed in the As Treated (AT) population (defined by the treatment actually received, rather than the treatment assigned). An additional analysis will be performed in the mAT population (defined by the treatment actually received, rather than the treatment assigned and excludes all subjects with prior statin therapy). ***Primary Safety Endpoint Analysis:*** Primary safety endpoints will be evaluated in the ITT population using appropriate descriptive statistics at discharge, 30 days, and 60 days from hospital admission. ***Powered Secondary Efficacy Endpoint Analysis:*** The secondary powered endpoint analysis will be a test of superiority of ***Colchicine + Rosuvastatin*** in addition to SOC compared to SOC alone assessed by the composite outcome of mechanical ventilation, any myocardial injury and death measured at 30 days. The sample size of 466 subjects (233 per group) will provide 85% power to test the secondary hypothesis assuming a 48% composite event rate at 30 days in the control group (based on internal data from YNHH), a 30% relative reduction in events with treatment, a 2-sided α=0.05 and 5% loss to follow-up at 30 days. The secondary endpoint will be evaluated in the ITT population (defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received). A secondary analysis will be performed in the AT population (defined by the treatment actually received, rather than the treatment assigned). An additional analysis will be performed in the mAT population (defined by the treatment actually received, rather than the treatment assigned and excludes all subjects with prior statin therapy). ***Secondary Endpoint Analysis*** All secondary endpoints will be evaluated in the ITT population using appropriate descriptive statistics at 30 and 60 days from hospital admission. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. Proportions of subjects with various scores on ordinal scales (i.e. WHO ordinal scale for clinical improvement) will be compared between groups using the Chi-squared test for the ordinal logistic regression model (null hypothesis states that the slope coefficients in the model are the same across response categories). As a secondary analysis, all secondary safety endpoints will be evaluated in the AT population. An additional analysis will be performed in the mAT population. **Secondary Imaging Endpoints**

	Secondary imaging endpoint based on cardiac MRI at 60 days will be performed in a subset of 50 subjects with documented reduced left ventricular ejection fraction and adjudicated suspected myocarditis during index hospitalization. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. ***Subgroup Analyses*** Subgroup analyses will be performed for all primary and secondary endpoints for the following subgroups: • Subject age (<65 years vs. ≥65 years) • Subject gender (males vs. females) • Presence of diabetes • Presence of hypertension • Presence of CAD • Presence of high-risk factors including CAD, HTN, cerebrovascular disease, CKD, heart failure. • Subjects naive to colchicine/statins prior to admission • Subjects receiving other medications as part of SOC (including antiplatelet agents, ACEi/ARB, dexamethasone, Remdesivir, tocilizumab, interferon-beta, therapeutic anticoagulation, etc.) • SOFA score tertiles on randomization • WHO score on randomization • Country and center of enrollment
Anticipated Timelines	First subject enrolled: October 2020 Last subject enrolled: June 2021 Final analysis: September 2021

3.0 Study Contacts

Sponsor

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4.0 Introduction

4.1 Background

Patients admitted to hospital with SARS-CoV-2 have a 30% likelihood of developing acute respiratory distress syndrome (ARDS), acute lung injury (ALI), or death, mediated through a cytokine release syndrome (CRS), associated with systemic inflammation, hemodynamic instability, and multiple organ failure. SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor. Upon entering the cells, SARS-CoV viroporins, transmembrane pore-forming viral proteins, may induce the activation of the NLRP3 inflammasome and production of pro-inflammatory cytokines, thought to contribute to the development of myocardial injury and ARDS/ALI.[3-7] Worldwide, COVID-19 is associated with higher morbidity and mortality among patients with underlying comorbidities. Modifying the host inflammatory response may help reduce COVID-19 complications as one observational study has demonstrated that treating COVID-19 ARDS patients with methylprednisolone significantly reduced mortality.[8]

Colchicine is an extensively studied and safe potent oral anti-inflammatory agent that was initially extracted from the autumn crocus. Colchicine inhibits tubulin polymerization and microtubule formation, which virtually brings to a halt any process that requires intracellular trafficking along microtubules, cell mitosis and cell migration.[9,10] Colchicine downregulates multiple inflammatory pathways and modulates innate immunity.[9,11] Importantly, colchicine interferes with the activation the NLRP3 inflammasome by disrupting the NLRP3 assembly or by inhibiting the polymerization of apoptosis-associated speck-like protein containing a caspase recruitment domain.[12-14] In addition, colchicine may interfere with SARS-CoV-2 viral endocytosis and disrupt the virus exit from the cell by preventing spike protein binding to microtubules.[15] Colchicine is currently being studied in multiple clinical trials as a stand-alone agent for the treatment of COVID-19 in the inpatient and outpatient setting.[16]

Colchicine is currently indicated for the treatment of gout, Behcet's syndrome, familial Mediterranean fever and pericarditis.[17,18] The cardiovascular benefits and safety profile of colchicine in the setting of secondary prevention therapy including high intensity statin therapy was demonstrated in two randomized controlled trials (RCTs): the Low-Dose Colchicine (LoDoCo) trial for patients with stable coronary disease[19], as well as in patients with a recent myocardial infarction in the COLCOT (Colchicine Cardiovascular Outcomes Trial).[20]

Statins are known to increase ACE2 expression in animals and humans[21-23], which may reduce the incidence of ARDS and improves survival.[24-27] In addition, statins have anti-inflammatory effects by antagonizing TLR-MYD88 pathways, often upregulated in severe SARS infection and by reducing inflammation-mediated endothelial dysfunction via Angpt/Tie2 signaling. Rosuvastatin, in particular, may have direct antiviral properties by binding and inhibiting the active site of the main protease enzyme (M^{pro}) of SARS-CoV-2. Consequently, it has been postulated that statin therapy may reduce the mortality of respiratory infections including Middle East Respiratory Syndrome (MERS) infection and several observational studies demonstrated that hospitalized patients on statin therapy have reduced morbidity and mortality associated with pneumonia.[28-30] Multiple RCTs have studied the use of moderate to high dose statin therapy in septic and/or intubated patients with variable results. [31-36] All studies verified the safety of statin usage and a few demonstrated efficacy with regards to various endpoints including mortality or

incidence of ventilator associated pneumonia[31], ICU length of stay[32], development of severe sepsis[36], and reduction in inflammatory cytokines [37]. However only two studies demonstrated efficacy with regards to their primary endpoint.[31,36] These differences may be because negative studies enrolled patients too late in their disease course. In line with this evidence, statins are being used in the treatment strategy of many COVID-19 patients (*de novo* use and continuation of chronic therapy).[38,39] One retrospective study published in a preprint has also demonstrated significant symptomatic benefit of chronic prior statin therapy in elderly patients infected with SARS-CoV-2.[40]

4.1.1 **Drug Combination Safety**

The long-term safety of the concurrent use of colchicine and high intensity statin therapy has been well established in two RCTs (>5000 patients total) studying colchicine in patients with coronary artery disease with low rates of adverse events – particularly infections, myopathy, and rhabdomyolysis (< 1-3% at 3 year follow-up).[19,20] Drug labels for both medications caution that use of both drugs can synergistically cause myopathy or rhabdomyolysis, especially in patients with renal impairment. However, rates of these events remain low in RCTs and observational studies and do not significantly differ from patients receiving only one of the medications; myositis resulted in withdrawal of <0.5% of patients in LoDoCo trial, there was no serious adverse event of myopathy reported in the COLCOT trial, and in a registry from South Korea (2.7% vs. 1.4%; p=0.3) of patients on colchicine and statin therapy vs. colchicine alone experienced myopathy while 0.3% vs. 0.5% experienced rhabdomyolosis.[19,20,41] There is no safety data currently available on concurrent use of both medications in COVID-19 patients.

4.2 Rationale

To reduce morbidity and mortality associated with acute respiratory distress syndrome (ARDS) and myocardial injury in patients with SARS-CoV-2 we propose to test a combined treatment of colchicine and statin in a randomized clinical trial.

4.3 Drug Description

Colchicine was approved in the US in 1961 for use in the prophylaxis and treatment of acute gout and familial Mediterranean fever, for which long-term administration is recommended. Extensive experience of this drug in clinical practice, established oral dosing and drug-drug interactions are well documented in the prescribing information.

Rosuvastatin is approved to reduce the risk of MI, stroke, revascularization, angina and to reduce total cholesterol and LDL-C, TG. There is extensive experience with this drug in clinical practice, with established oral dosing and drug-drug interactions are well documented in the prescribing information. Rosuvastatin is contraindicated in patients with hypersensitivity reactions, active liver disease, pregnancy, or nursing. Myopathy is increased with use of strong CYP3A4 inhibitors and protease inhibitors and requires dose adjustment (section §7.4.1). Elevation of liver enzymes was reported in 2.3% of cases and resolves with discontinuation. Other reported adverse reactions include myalgia, abdominal pain and nausea.

4.4 Regulatory Status

Both drugs have been in use for decades for gout and pericarditis (colchicine) and hyperlipidemia, coronary disease and diabetes (rosuvastatin), and tested in thousands of patients with a low but well characterized risk profile.

Colchicine and rosuvastatin are currently used as standard of care in COVID-19 patients whether due to pre-existing disease or acute presentations with acute coronary syndromes or acute gout and we do not expect added risk in the population being studied.

This study is not intended to support a labeling change for a new indication for use or significant safety change or advertising claim for either drug, and the study will be conducted in compliance with the requirements of the Yale institutional review board (IRB), the ethics/regulatory bodies of international participating centers, and of the Research investigational new drug application (IND).

5.0 Study Design

The Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial is a pragmatic randomized open-label study to evaluate the safety and efficacy of the combination of ***Colchicine*** + **Rosuvastatin** in addition to standard of care (SOC) compared to SOC alone in hospitalized patients with SARS-CoV-2.

5.1 Study Design Overview

Subjects will be screened within 48 hours of hospital admission. A total of 466 subjects with RT-PCR confirmed SARS-CoV-2 infection meeting all inclusion and no exclusion criteria, will be randomized to either ***Colchicine*** + **Rosuvastatin** treatment added to SOC or SOC alone for the duration of hospitalization. SOC will be guided by the Yale New Haven Health SARS-CoV-2 Therapeutics Group. Subjects will be assessed daily while hospitalized for clinical, biomarker, safety, and laboratory parameters based on the YNHH SOC algorithm. Study treatment will be continued for 30 days or until hospital discharge whichever occurs sooner. The subjects will be followed clinically until hospital discharge, at 30 days and 60 days from randomization. After discharge follow-up will be by phone (Figure 1). A subset of 50 patients with CEC adjudicated suspected myocarditis and new reduced LVEF (>10% reduction) by in hospital echocardiography will undergo cardiac MRI at 60 days for assessment

Figure 1. COLSTAT Trial Design

5.2 Study Objectives

To investigate the safety and efficacy of the combination of ***Colchicine*** + **Rosuvastatin** added to standard of care (SOC) compared to SOC alone in hospitalized subjects with moderate COVID-19.

5.3 Study Endpoints

5.3.1 **Primary Endpoints**

5.3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be a 30 day composite of the following:

1) Progression of COVID-19 disease as defined by the World Health Organization (WHO) Ordinal Scale for Clinical Improvement Scores 5-8 (or 6-8 if patient at score of 5 at time of randomization)*.
2) Arterial or Venous thromboembolic complications confirmed by imaging (including DVT/PE, MI, and ischemic stroke).

*WHO ordinal Scale:

- *Score 5*: Hospitalized requiring non-invasive ventilation or high-flow oxygen/high-flow nasal cannula
- *Score 6:* Hospitalized requiring intubation and mechanical ventilation
- *Score 7*: Hospitalized requiring ventilation and additional organ support (vasopressors, renal replacement therapy, ECMO)
- *Score 8*: Death

5.3.1.2 Primary Safety Endpoint

The primary safety endpoint will be the proportion of subjects with treatment emergent adverse events (TEAE) defined as undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

5.3.2 **Secondary Endpoints**

5.3.2.1 Powered Secondary Efficacy Endpoint

The secondary powered efficacy endpoint will be a composite outcome assessed at 30 days including:

a. Respiratory failure requiring invasive mechanical ventilation,
b. Any myocardial injury (troponin URL> 99th percentile or ≥2-fold increase if troponin is abnormal at baseline or a new >10% reduction in LVEF by Echocardiography)
c. Death

5.3.2.2 Secondary Endpoints

The following secondary endpoints will be reported by treatment group at 30 and 60 days:

Clinical Safety and Efficacy:

a. Death (all cause and cardiovascular)
b. Duration of oxygen therapy (days)
c. Duration of invasive mechanical ventilation (days)
d. Duration of intensive care treatment (days)
e. Duration of hospitalization (days)
f. Any myocardial injury (troponin URL > 99^{th} percentile or a $\geq$2-fold increase if troponin is abnormal at baseline or a new >10% reduction in LVEF by Echocardiography), and

underlying ischemic (Fourth Universal definitions) or inflammatory cause

g. Venous thrombosis or thromboembolic complication confirmed by imaging
h. All stroke (NeuroARC defined)
i. Acute kidney injury (AKIN criteria)
j. Time (in days) to symptomatic improvement: reduction in baseline WHO ordinal score by >2 points or achievement of scores 1-3.
k. Overall WHO ordinal scale for clinical improvement at 30 and 60 days.

Other Secondary Biomarker Endpoints:

a. Sequential Organ Failure Assessment (SOFA) score, defined by 6 variables (the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems) scored from 0 (normal) to 4 (high degree of dysfunction/failure).
b. Change of the SOFA from baseline.
c. Peak and change from baseline in routine biomarkers (CRP, procalcitonin, D-dimer, PTT/INR, ferritin, troponin/CK-MB, BNP, CPK, AST, ALT, ALP, bilirubin, white blood cell count), as available.
d. Peak and change from baseline in cytokine panel (IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available

*If an arterial blood gas (ABG) is not available to calculate the PaO2/FiO2 ratio for the SOFA assessment the SpO2/FiO2 ratio may be used as an alternative per prior literature.[2]

Secondary Imaging Endpoints (Imaging substudy)

a. Proportion of subjects with reduction in LVEF defined as a decrease of more than 10% in LVEF by a clinically driven point of care echocardiography measured in hospital
b. Cardiac MRI in a subset of subjects with adjudicated suspected myocarditis assessed at 60 days.

6.0 Subject Selection and Withdrawal

6.1 Patient Population

A total of 466 adult subjects with RT-PCR confirmed SARS-CoV-2 infection hospitalized with moderate (non ICU) COVID-19 will be recruited within 48 hours of admission.

6.2 Eligibility Criteria

6.2.1 **Inclusion Criteria**

Subjects must meet ALL of the following criteria to be eligible for inclusion in the study:

1. 18 years or older and confirmed SARS-CoV-2 infection by RT-PCR
2. Patient is admitted to the floor or step down (non-ICU) within 72 hours of hospital admission

3. The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions and has provided witnessed (by 2 independent members of the health care team) oral informed consent, or a photograph of the signed informed consent approved by the appropriate Institutional Review Board (IRB)

6.2.2 **Exclusion Criteria**

Subjects will be excluded if ANY of the following criteria apply:

1. Known pregnancy or nursing mothers
2. Known allergy to statins or colchicine
3. Patient is on chronic colchicine
4. Acute liver disease defined by elevated transaminases (AST/ALT > 3x ULN)
5. Severe chronic kidney disease defined as glomerular filtration rate (GFR) < 30mL/min1.73 m^2
6. Severe QTc prolongation (>500ms narrow QRS<120ms and >550ms for wide QRS>120)
7. Presents with severe disease on admission requiring ICU admission (WHO ordinal scale of clinical improvement scores 6-8)
8. Rhabdomyolysis or CPK > 5x ULN
9. Thrombocytopenia defined as platelet count < 50,000 / mm^3
10. Leukopenia defined as white blood cell count < 2,500/ μl
11. Severe anemia defined as Hemoglobin value <8 g/100ml
12. Participation in any other clinical trial of an experimental treatment for COVID-19

6.3 Subject Screening

All COVID-19 positive patients older than 18 years of age identified through EPIC will be screened for enrollment. All potential subjects will be screened by study coordinators in consultation with the treating clinicians for eligibility in the COLSTAT trial. After confirmation of clinical diagnosis of SARS-CoV-2, the research coordinator will review all inclusion and exclusion criteria.

6.4 Informed Consent

Subjects will be recruited from the Yale New Haven Hospital (YNHH) and health system. Subjects confirmed SARS-CoV-2 positive older than 18 years of age will be offered participation in the study using a verbal consent witnessed by 2 health care professionals to limit unnecessary handling of forms, or a photograph of the signed informed consent approved by the Institutional Review Board (IRB). Video consenting will be implemented whenever possible to limit direct patient exposure. The informed consent and HIPAA authorization will be obtained prior to patient participation in this trial. The overall protocol (including objectives, procedures and duration), potential risks and benefits, voluntary nature and ability to withdraw will be discussed and reviewed with each patient and/or their legally authorized representative. The patient and/or their

legally authorized representative will be given a copy of the IRB-approved ICF to review and will have all questions answered before being asked to provide verbal consent witnessed by 2 health care providers. Verification of comprehension of the consent will be obtained by asking the subject to describe in their words the purpose and risks of the study. The patient and/or their legally authorized representative will be instructed that his or her care will not be affected by his or her decision to participate, or not. If the patient and/or their legally authorized representative voluntarily agrees to participate in the trial, he or she will be asked to provide a verbal consent witnessed by 2 healthcare providers (coordinator and physician or nurse) and consent will be documented in EPIC by the research coordinator, health care provider or principal investigator.

Study subjects and/or their legally authorized representatives will be considered to have capacity to provide informed consent if they provide comprehensible and sensible answers to the following questions:

(1) Tell me what will happen if you agree to partake in this study?

(2) Can you leave this study once it begins?

(3) What should you do if you want to stop being in this study?

6.5 Subject Enrollment and Randomization

Subjects meeting eligibility criteria and providing informed consent will be randomized to ***Colchicine*** 0.6mg twice daily for 3 days followed by 0.6mg daily + **Rosuvastatin** 40mg daily in addition to SOC or SOC only using electronic block randomization programed within EPIC. Investigational treatment will continue until hospital discharge.

Randomized patients will undergo management based on standard of care treatment determined by the primary care team and the YNHH treatment algorithm for hospitalized patients with COVID-19. Baseline screening will include History & Physical (H&P), chest X-ray (CXR), and baseline ECG. SOFA score including Glasgow coma score will be preferably be recorded every 24 hours as able. Baseline biomarker measurements and subsequent frequency will be based on each center's SOC but preferably should occur every 24 hours during hospitalization and should preferably include at minimum a basic metabolic panel, CBC with differential, LFTs, CRP, procalcitonin, D-dimer, and troponin (or CK-MB if not available). Cytokine measurement and other labs/imaging will occur according to the SOC of each center.

6.6 Withdrawal and Replacement of Subjects

Subjects can withdraw from the study at any time; the reason(s) for withdrawal (if given) will be documented. All data available at the time of withdrawal (if any) will be used for analysis. There will be no further follow-up (per this study protocol) on subjects who have withdrawn. Subjects who withdraw from the study will not be replaced. The withdrawal of a subject can be initiated by the Investigator if he/she determines it is in the best interest of the patient.

6.7 Protocol Deviations

All deviations from the requirements of this Clinical Investigation Plan will be considered protocol deviations.

A major protocol deviation is a protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients. Major protocol deviations require urgent reporting to the Study Monitor and the Institutional Review Board.

Patient-level deviations are those that occur in direct association with a specific study patient. These include, but are not limited to, deviations from informed consent procedures, inclusion/exclusion criteria, protocol-specified procedures and assessments, and drug handling and usage.

Site-level deviations are those that occur at the study center but are not directly related to a study specific patient. All efforts shall be made to avoid any protocol deviation.

7.0 Study Procedures

7.1 Study Schedule of Procedures and Assessment

Randomized subjects will undergo management based on standard of care. Baseline screening will include History & Physical (H&P), chest X-ray (CXR), and baseline ECG as clinically indicated. SOFA score including Glasgow coma score will be recorded preferably every 24 hours as able. Baseline biomarker measurements and subsequent frequency will be based on each center's SOC but preferably should occur every 24 hours during hospitalization and preferably should include at minimum a basic metabolic panel, CBC with differential, LFTs, CRP, procalcitonin, D-dimer, and troponin (or CK-MB if not available). Cytokine measurement and other labs/imaging will occur according to the SOC of each center.

Table 1. Study Schedule of Procedures and Assessments

Visit Identifier .	**Screening**	**Day 1**	**Daily Assessments**						**End of Treatment (Discharge)**	**30 day follow-up (by phone)**	**60 day follow-up (by phone)**	**Follow-up (30 days post-discharge) Cardiac MRI subgroup**
Visit Window												
Informed consent	X											
Randomization		X										
Medical history	X											
Physical examination	X	X	X	X	X	X	X	X	X			
Height/Weight*	X											
ECG**	X											
Chest X ray**	X											
Vital signs (pulse, blood pressure, respiratory rate, SpO2 by pulse oximetry, temperature)	X	X	X	X	X	X	X	X	X			
Laboratory[1]												
Hematology	X	X	X	X	X	X	X	X	X			

Visit Identifier .	Screening	Day 1	Daily Assessments						End of Treatment (Discharge)	30 day follow-up (by phone)	60 day follow-up (by phone)	Follow-up (30 days post-discharge) Cardiac MRI subgroup
Visit Window												
Blood chemistry	X	X	X	X	X	X	X	X	X			
Inflammation panel[2]	X	X	X	X	X	X	X	X	X			
Coagulation[3]	X	X	X	X	X	X	X	X	X			
Cardiac panel[4]	X	X	X	X	X	X	X	X	X			
Liver function test	X	X	X	X	X	X	X	X	X			
Arterial blood gas*												
Record if admitted to intensive care unit (ICU)		X	X	X	X	X	X	X	X			
Assessments			X	X	X	X	X	X	X			
Efficacy:	X	X	X	X	X	X	X	X	X			
FiO2	X	X	X	X	X	X	X	X	X			
WHO Ordinal scale of clinical improvement	X	X	X	X	X	X	X	X	X			
SOFA score ***	X	X	X	X	X	X	X	X	X			
Assessment of level of consciousness	X	X	X	X	X	X	X	X	X			
Cytokine panel[5]		X		X		X		X	X			
Test for SARS-CoV2[6]	X											
Concomitant treatment(s)		X	X	X	X	X	X	X	X	X		
Hand-held Echo**		X	X	X	X	X	X	X				
Serious and nonserious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	
Hospital Readmission										X	X	
Cardiac MRI												X

*As clinically indicated

** Diagnostics including ECG, Chest X-ray, and echo should occur according to each centers SOC as clinically indicated. It is preferably but not required if every patient has baseline ECG and Chest X-ray. If a patient is suspected of having myocarditis due to rise an cardiac enzymes or clinical signs it is

recommended but not required that they receive a point of care echo if within center's SOC. Further imaging is not mandated and should only occur as clinically indicated.
*** The SOFA score requires LFTs, creatinine, and an ABG. It should be recorded for every patient when appropriate labs are available within a 24 hour period. If and ABG is not available to assess PaO2/FiO2 it is okay to substitute using SpO2/FiO2 ratio per prior literature. See definitions in Section 15.1.

We will collect serum samples for biobanking. Samples will be obtained at Day 1 prior to treatment administration and then every 72 hours thereafter until discharge (see Figure 1. COLSTAT Trial Design). All biomarker measurements and subsequent imaging/tests will occur based on SOC at respective center and decision of primary team when clinically indicated. However, preferably should occur every 24 hours during hospitalization and preferably should include at minimum a basic metabolic panel, CBC with differential, LFTs, CRP, procalcitonin, D-dimer, and troponin (or CK-MB if not available). Cytokine measurement and other labs/imaging will occur according to the SOC of each center.

[1]Routine labs should occur per center's SOC, preferably should occur at least every 24 hours and preferably should include at minimum a basic metabolic panel, CBC with differential, LFTs, CRP, procalcitonin, D-dimer, and troponin (or CK-MB if not available). BNP, ferritin, LDH, PTT/INR are useful parameters that may also be measured based on SOC and clinical indication when appropriate.

[2] Inflammatory panel per center's SOC: preferably CRP and procalcitonin should be measured every 24 hours. If Cytokines are measured in hospital per SOC it would be preferably to measure IL-1, IL-6, and TNF-α at minimum, preferably on day 1, day 3, day 7/discharge, and if patient is transferred to the MICU. IL-2, IL-8, IL-17A, IL-17F, IP-10, CCL5, ferritin, and LDH may also be useful and may be measured based on center's SOC when clinically indicated.

[3] Coagulation panel per center's SOC: Preferably D-dimer should be measured every 24-48 hours at minimum. Fibrinogen, PT/PTT may also be measured based on center's SOC

[4] Cardiac panel per center's SOC: Preferably quantitative troponin (or CK-MB when troponin not available) should be measured every 24-48 hoors at minimum. BNP and LDH may also be measured based on center's SOC

[5] Cytokine panel per center's SOC: IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5 may be measured if part of center's SOC. If Cytokines are measured in hospital per SOC it would be preferably to measure IL-1, IL-6, and TNF-α at minimum, preferably on day 1, day 3, day 7/discharge, and if patient is transferred to the MICU.

[6] Test for SARS-CoV2 by real time reverse transcription polymerase chain reaction RT-PCR. Mandated to occur before enrollment. Retesting to occur based on center's SOC

7.2 Screening / Baseline

Subjects will be recruited from the Yale New Haven Hospital (YNHH) and health system. Subjects will be screened within 48 hours of admission for SARS-CoV-2. Informed consent will be obtained after confirmation of COVID-19 positivity by RT-PCR and eligibility criteria. Subjects will not be compensated.

Screening for enrollment in the study will include subject information and all standard of care (SOC) in the evaluation of patients with SARS-CoV-2. Subjects will be excluded for known pregnancy, known hypersensitivity to statins or colchicine, if they are on chronic colchicine or oral corticosteroid treatment, liver failure, severe kidney disease (glomerular filtration rate (GFR) < 30mL/min), prolonged QTc, requiring intubation on admission.

7.3 Concomitant Therapies

Selection and dosing of concomitant therapies, all standard of care treatments for hospitalized patients with SARS-CoV-2 are permitted during the period of treatment with the study intervention. This only includes treatments approved by the Yale SOC treatment Committee. Concomitant therapy will be performed according to standard practice, local standards of care and published guidelines. Subjects will not be permitted to participate in other investigational studies.

All medications administered will be recorded in the patient's medical record.

7.4 Drug Dosing, Storage and Discontinuation

7.4.1 **Drug Dosing**

In addition to standard of care patients randomized to active treatment will receive:

- **Rosuvastatin: 40mg daily AND**
- **Colchicine: 0.6mg twice daily for 3 days then 0.6mg daily**

Note: Subjects previously on chronic statin therapy will be eligible for enrollment in the trial, and if randomized to active treatment, chronic statin therapy will be discontinued and replaced by rosuvastatin 40 mg for 30 days or hospital discharge and resumed thereafter.

7.4.1.1 Drug Interactions and Dosing Adjustment

Note: for subjects taking drugs with interaction with colchicine the dose will be reduced according to the following:

- Co-administration with Strong CYP3A4 Inhibitors (includes Atazanvir): 0.3mg once a day X3 days then 0.3mg every other day
- Co-administration with Moderate CYP3A4 Inhibitors (includes Erythromycin, Diltiazem, Verapamil, Fosamprenavir): 0.3mg twice a day X3 days then 0.3mg every day
- Co-administered with Protease Inhibitors (atazanavir, Darunavir, Indinavir, Ritonavir, saquinavir, Tipranavir, Nelfinavir) 0.3mg once a day X3 days then 0.3mg every other day

Drug interactions will be screened throughout hospitalization and active treatment and will be programmed in EPIC to notify the treatment team and research coordinator. All standard of care treatments for hospitalized patients with SARS-COV-19 are permitted during the period of treatment with study intervention. Dose adjustments for drug interactions are listed above. Drug discontinuation is only permitted with documented adverse reactions. The standard of care treatment will be determined by the primary care team and the YNHH treatment algorithm for hospitalized patients with COVID-19.

7.4.1.2 Dose Modification and Renal Impairment

- Patients who develop mild or moderate renal impairment (estimated GFR >30 mL/Min) will be monitored for adverse effects. Dose reduction of colchicine may be necessary.
- Patients with severe renal impairment (estimated GFR < 30mL/Min)
    - Recommended colchicine dose is 0.3mg twice a day X3 days then 0.3mg every day and should be monitored closely for adverse effects of colchicine
    - Recommended rosuvastatin dose is 10 mg daily

7.4.1.3 Dose Modification and Hepatic Impairment

- Patients with or who develop mild or severe hepatic impairment should be monitored closely for adverse effects of colchicine and rosuvastatin
- Patients with severe hepatic impairment,
    - recommended dose is 0.3mg twice a day X3 days then 0.3mg every day and should be monitored closely for adverse effects of colchicine
    - Recommend discontinuation of rosuvastatin

7.4.2 **Drug Storage**

Commercially available tablets will be stored at and dispensed by the YNHH pharmacy. The tablets or suspension can be given by mouth or via nasogastric tube. The pharmacy may convert the active ingredient into a suspension form.

7.4.3 **Drug Discontinuation**

Study drug may be discontinued in a subject after review of all available data with the medical monitor and discussion with the investigator if any of the following occur:

- Any SAE or $\geq$ Grade 3 AE is suspected to be related to treatment
- Any elevation of ALT>5xULN confirmed by repeat testing
- Any elevation of CK >5xULN confirmed by repeat testing
- Severe myalgias suspected related to statin therapy
- Subjects who develop renal or hepatic impairment and require a protease inhibitor or strong CYP3A4 inhibitor should discontinue colchicine

- Subjects who develop new blood dyscrasia including leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia should discontinue colchicine

7.5 In-hospital Follow-up

Randomized subjects will be assessed daily while hospitalized for clinical, cardiac and inflammatory biomarkers, safety, and laboratory parameters based on SOC.

8.0 Adverse Events and Serious Adverse Events

Adverse events will be reviewed by the DSMB. Both treatment drugs are approved and commonly prescribed. The trial is open labeled and driven by standard of care. We will therefore monitor discontinuations of treatment and the underlying reasons to monitor adverse events attributable to treatment.

8.1 Adverse Events (AE)

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event could present as an abnormal laboratory finding, abnormal imaging finding or an abnormal clinical finding or symptom.

8.2 Life-threatening Adverse Event *or* Life-threatening Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.3 Serious Adverse Events (SAE) *or* Serious Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4 Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

For rosuvastatin, these may include (2%)

- Myalgia
- Abdominal pain
- Nausea
- Headache

For cochicine, these may include (up to 20%):

- Abdominal pain
- Nausea
- Diarrhea
- Vomiting
- Rash
- Elevated AST/ALT
- Myopathy

8.5 Unexpected Adverse Event *or* Unexpected Suspected Adverse Reactions

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.6 Documentation

Adverse events must be listed on the patient's medical record. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

8.6.1 **Intensity or Severity**

The following grades of the intensity of an adverse event will be used, according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0[42]:

Grade 1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	**Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	**Life-threatening** consequences; urgent intervention indicated
Grade 5	**Death** related to AE.
ADL=Activities of Daily Living; *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

8.6.2 **Relatedness**

The investigator will use the following definitions to assess the relationship to the treatment:

Not related	The cause of the AE is known, and the event is not related to any aspect of study participation.
Unlikely to be related	There is little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by study participation. The AE has a **timely relationship** to the study procedure(s); **however, follows no known pattern of response**, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.

Probably related	It is likely that the event was caused by study participation. The AE has a **timely relationship** to the study treatment and **follows a known pattern of response**; a potential alternative cause, however, may explain the event.
Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

If the relationship between any adverse event and the use of the investigational drug is considered to be possibly or probably related, that event will be classified as an ADE or SAE

8.6.3 **Outcome**

The clinical outcome of the AE or SAE will be characterized as follows:

Death	The SAE CRF must be completed for this outcome
Recovered without sequelae	The patient returned to baseline status
Ongoing	Patient did not recover and symptoms continue
Recovered with sequelae	The patient has recovered but with clinical sequelae from the event
Unknown	The patient outcome is unknown

8.6.4 **Treatment or Action Taken**

The treatment or action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment	Surgical, percutaneous or other procedure
Medical Treatment	Medication dose reduction/interruption or discontinuation, or medication initiated for event
None	No action is taken

8.7 Reporting

8.7.1 **General Adverse Event Reporting Procedures**

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug; and b) other unanticipated problems involving risks to subjects or others. These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710.

8.7.1.1 Safety Reports Submitted to FDA

For studies conducted under an IND, there are two types of Safety Reports submitted to FDA:

- 7-Calendar-Day FDA Telephone or Fax Report: The sponsor-investigator will directly notify the FDA, within 7 calendar days after initial receipt of the information, of any adverse event that is fatal or life-threatening, unexpected, and considered at least possibly related to the investigational product.
- 15-Calendar-Day FDA Written Report: The sponsor-investigator will directly notify the FDA within 15 calendar days after initial receipt of the information, of any serious adverse event (other than those that are fatal or life-threatening) that is unexpected and considered at least possibly related to the investigational product.

Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

8.7.2 **Serious Adverse Events**

The Principal Investigator will notify the Yale IRB within 3 working days of first learning of any SAE using the EDC CRF. If necessary, the Investigator may be requested to provide copies of de-identified source documentation (e.g., physician/nurse notes or summaries) regarding the event. If required, SAEs will be reported by YALE to the applicable authority.

8.7.3 **Unexpected Adverse Event *or* Unexpected Suspected Adverse Reaction**

The Principal Investigator will notify the Yale IRB within 3 working days of first learning of any unexpected adverse event *or* unexpected suspected adverse reaction using the EDC CRF. If necessary, the Investigator may be requested to provide copies of de-identified source documentation (e.g., physician/nurse notes or summaries) regarding the event. If required, unexpected adverse event *or* unexpected suspected adverse reaction will be reported by YALE to the applicable authority.

8.7.3.1 Expected Adverse Events

The following adverse events have been identified as actual or potential complications associated with colchicine and rosuvastatin therapy.

Risks reported with colchicine:

- Rhabdomyolysis
- Neuromuscular toxicity
- Renal and hepatic toxicity
- Disseminated intravascular coagulation
- Diarrhea
- Pharyngolaryngeal pain
- Nausea
- Abdominal pain
- vomiting
- fatigue
- Headache
- Leukopenia
- Granulocytopenia
- Thrombocytopenia
- Pancytopenia

- Myopathy
- Elevated CPK

Risks reported with rosuvastatin:

- Myalgia
- Abdominal pain
- Nausea
- Headache
- Rhabdomyolysis
- Liver enzymes abnormalities
- Constipation

Frequencies of common side effects by dose of each of these drugs are shown in Table 2 and 3 below:

Table 2: Colchicine: Number (%) of Patients with at Least One Drug-Related Treatment-Emergent Adverse Event with an Incidence of >2% of Patients in Any Treatment Group

MedDRA System Organ Class MedDRA Preferred Term	COLCRYS Dose		Placebo (N=59) n (%)
	High (N=52) n (%)	Low (N=74) n (%)	
Number of Patients with at Least One Drug-Related TEAE	40 (77)	27 (37)	16 (27)
Gastrointestinal Disorders	40 (77)	19 (26)	12 (20)
Diarrhea	40 (77)	17 (23)	8 (14)
Nausea	9 (17)	3 (4)	3 (5)
Vomiting	9 (17)	0	0
Abdominal Discomfort	0	0	2 (3)
General Disorders and Administration Site Conditions	4 (8)	1 (1)	1 (2)
Fatigue	2 (4)	1 (1)	1 (2)
Metabolic and Nutrition Disorders	0	3 (4)	2 (3)
Gout	0	3 (4)	1 (2)
Nervous System Disorders	1 (2)	1 (1.4)	2 (3)
Headache	1 (2)	1 (1)	2 (3)
Respiratory Thoracic Mediastinal Disorders	1 (2)	2 (3)	0
Pharyngolaryngeal Pain	1 (2)	2 (3)	0

Table 3: Rosuvastatin: Adverse Reactions* Reported by ≥ 2% of Patients Treated with CRESTOR and > Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	CRESTOR 40 mg N=700	Placebo N=281
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3
Dizziness	4.0	2.8
Increased CPK	2.6	0.7
Abdominal pain	2.4	1.8
†ALT >3x ULN	2.2	0.7

* Adverse reactions by MedDRA preferred term.

† Frequency recorded as abnormal laboratory value.

9.0 Benefit: Risk Analysis

9.1 Potential Benefits

We estimate from data collected by the Yale New Haven Health System (including 1,412 COVID-19 patients) that hospitalized patients with SARS-COV-19 have a 48% risk of requiring mechanical ventilation, myocardial injury or death. Based on prior literature we estimate a 30% benefit from the use of ***Colchicine*** + **Rosuvastatin** started early during admission. If proven beneficial, the enrolled subjects will have a direct benefit in reducing complication rate and other subsequent patients hospitalized with SARS-COV-19 will also benefit from a proven treatment of this morbid and sometimes fatal disease.

Because the drug combination ***Colchicine*** + **Rosuvastatin** is low risk and cheap, this treatment can be implemented early with significant impact on clinical outcomes.

The trial is expected to make a substantial contribution to medical science and clinical decision-making that could benefit future patients with SARS-CoV-2.

9.2 Potential Risks and Discomforts

Both ***Colchicine*** and **Rosuvastatin** have been extensively studied in thousands of patients used individually and in combination with a low and well characterized risk profile. Colchicine and rosuvastatin are currently used as standard of care in COVID-19 patients whether due to pre-existing CAD, gout or pericarditis or acute presentations with acute coronary syndromes or acute gout with no expected added risk in the population being studied. Because both drugs are used in combination in COVID-19 positive patients the potential risk is deemed low/moderate, however has not been evaluated previously.

9.3 Methods to Minimize Risks

Patients will be evaluated at least once daily depending on level of acuity. Daily laboratory monitoring including CBC, CMP are all included in the standard of care. In addition, CPK will be monitored with symptoms of muscle pain. Patients at risk for drug complications are excluded from the study (sever liver disease and severe kidney disease).

10.0 Study Committee

10.1 Executive Committee

The executive committee will be comprised of the principal investigator, co-investigators and sub-investigators. They will convene on a monthly basis to review enrolment and compliance with the protocol and provide guidance for the conduct of the trial.

10.2 Clinical Events Committee

An independent Clinical Events Committee (CEC), or Independent Physician Adjudicator, will be responsible for systematic review and adjudication of all primary and secondary safety events as identified in this protocol to ensure uniform classification of events according to pre-specified definitions as well as relationship to the drug(s) or combination of drugs versus underlying disease. Clinical experts will be selected based upon their expertise with cardiovascular disease, infectious disease, renal disease and or neurological disease therapeutic areas as well as their expertise and familiarity with the growing body of knowledge regarding SARS-CoV-2.

In order to enhance objectivity and reduce the potential for bias, the CEC members shall be independent of direct treatment of subjects enrolled under this research protocol. The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter. Operational provisions shall be established to minimize potential bias.

10.3 Data Safety Monitoring Board

An independent data safety monitoring board will oversee the safe and ethical conduct of the trial. The DSMB will have the authority to discontinue the trial on the basis of safety concerns. Given the current unknown effect of multiple treatment effects, emerging treatment interventions and the evolving knowledge of the course and impact of SARS-CoV-2 on public and individual subject health and safety, the DSMB may comment or advise the Sponsor on potential signs of futility.

Adverse events will be reviewed by the DSMB. Both treatment drugs are approved and commonly prescribed. The trial is open labeled and driven by standard of care.

DSMB will therefore monitor discontinuations of treatment and the underlying reasons to monitor adverse events attributable to treatment.

10.3.1 **Considerations for Stopping Rules**

The DSMB may consider making a recommendation for a temporary hold on enrollment and further randomization should any of the following be observed:

- A two-fold increase in event rates for key events of special interest is seen in the treatment arm versus the control arm, or a two-fold increase in serious adverse events overall is seen in the treatment arm versus the control arm.

Key events of special interest for the purpose of DSMB evaluation include:

- Elevations in hepatic transaminases
- Myopathies
- Myalgia
- Asthenia
- Rhabdomyolysis
- Impaired renal function as evidenced by change in either serum creatinine or creatinine clearance
- Gastrointestinal adverse events including nausea, vomiting or diarrhea
- Death
- Thrombosis or thromboembolic events

The DSMC shall conduct a full investigation of potential contributing causes prior to making any recommendation for enrollment to resume, a change to protocol, or termination of further enrollment or randomization.

The DMC reserves the right to make a recommendation for temporary suspension of enrollment until circumstances are investigated should the number of deaths reported to the committee in an expedited fashion appear higher in the treatment arm than the number reported in the control arm or if >5 unanticipated suspected adverse reactions are reported via expedited event reporting.

11.0 Statistical Considerations and Analysis Plan

11.1 Hypotheses

The COLSTAT Trial will test the following hypotheses:

Primary Hypothesis: Among hospitalized SARS-CoV-2 confirmed subjects treated with standard therapy, the addition of ***Colchicine*** **+ Rosuvastatin** is superior to standard of care in reducing the composite outcome of progression to severe COVID-19 disease (as defined by WHO ordinal scale scores 5-8 or 6-8 if at score of 5 on admission) and arterial and venous thromboembolic complications at 30 days.

Secondary Powered Endpoint: Among hospitalized SARS-CoV-2 confirmed subjects

treated with standard therapy, the addition of ***Colchicine* + Rosuvastatin** is superior to standard of care in reducing the composite outcome of respiratory failure requiring mechanical ventilation, myocardial injury or death at 30 days.

Secondary Hypothesis: Among hospitalized SARS-CoV-2 confirmed subjects treated with standard therapy, the addition of ***Colchicine* + Rosuvastatin** reduces length of stay, need and duration of ICU care, myocardial injury, respiratory failure and duration, multiorgan failure or death, acute kidney injury, use of Extracorporeal Membrane Oxygenation (ECMO) and cytokine, inflammatory and cardiac biomarkers compared to standard of care measured at hospital discharge.

To determine the treatment effect in subgroup analysis (test of interaction) and predictors of the secondary powered endpoint of mechanical ventilation, myocardial injury or death among candidate variables including baseline risk factors, cytokines, inflammatory and cardiac biomarkers. We hypothesize that ***Colchicine* + Rosuvastatin** will have a consistent treatment effect across all subgroups.

Among subjects who develop myocardial injury during hospitalization, ***Colchicine* + Rosuvastatin** compared to standard of care will improve cardiac function and recovery based on 30-day post discharge cardiac Magnetic Resonance Imaging (MRI).

11.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint hypothesis is a test of superiority of ***Colchicine* + Rosuvastatin** in addition of SOC compared to SOC alone assessed by the primary composite outcome of progression to severe COVID-19 disease (as defined by WHO ordinal scale scores 5-8) at 30 days. Specifically, the superiority hypotheses are

$$H0: P1 - P2 = 0 \text{ vs. } H1: P1-P2 \neq 0$$

Where:

P1 = the true rate of primary endpoint at 30 days in the ***Colchicine*** + **Rosuvastatin** in addition to SOC arm

P2 = the true rate of primary endpoint at 30 days in the SOC only arm

The null hypothesis will be tested at a two-sided 0.05 level of significance and using the two-sample proportion test. Superiority will be demonstrated if the true primary outcome of progression to severe COVID-19 disease are not equal using the two-proportion tests.

11.1.2 Powered Secondary Endpoint

The powered secondary efficacy endpoint analysis will be a test of superiority of ***Colchicine*** + **Rosuvastatin** in addition to SOC compared to SOC alone assessed by the composite outcome of mechanical ventilation, myocardial injury and death measured at 30 days. Specifically, the superiority hypotheses are:

$$H0: P1 - P2 = 0 \text{ vs. } H1: P1-P2 \neq 0$$

Where:

P1 = the true rate of composite outcome of mechanical ventilation, myocardial injury and death in the ***Colchicine*** + **Rosuvastatin** in addition to SOC arm

P2 = the true rate of composite outcome of mechanical ventilation, myocardial injury and death in the SOC only arm

The null hypothesis will be tested at a two-sided 0.05 level of significance and using the two-sample proportion likelihood test. Superiority will be demonstrated if the true composite primary outcome of mechanical ventilation, myocardial injury and death rates are not equal using the two-proportion tests.

11.2 Analysis Population

11.2.1 **Intention to Treat (ITT) Analysis Population**

The Intention to Treat (ITT) analysis population is defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received.

The ITT population will be the primary analysis population for all primary and secondary endpoints

11.2.2 **As Treated (AT) Analysis Population**

The As Treated (AT) analysis population is defined by the treatment actually received, rather than the treatment assigned.

The AT population is the secondary analysis population for all primary and secondary endpoints.

11.2.3 **M As Treated (mAT) Analysis Population**

The mAT analysis population is defined by the treatment actually received, rather than the treatment assigned and excludes all subjects with prior statin therapy.

The mAT population is an additional analysis population for all primary and secondary endpoints.

11.3 Sample Size Calculation and Assumptions

11.3.1 **Primary Endpoint Analysis**

The primary efficacy endpoint hypothesis is a test of superiority of ***Colchicine* + Rosuvastatin** in addition of SOC compared to SOC alone assessed by the primary outcome of progression to severe COVID-19 disease (as defined by WHO ordinal scale scores 5-8 or 6-8 if patient at score of 5 at time of randomization) and arterial and venous thromboembolic complications at 30 days. The primary endpoint will be evaluated in the ITT population. A secondary analysis will be performed in the AT population.

The following assumptions were made:

- Expected rate of the primary outcome of progression to severe COVID-19 disease (as defined by WHO ordinal scale scores 5-8) in the SOC alone arm at 30 days= 44.2%
- Assumes the true rates of primary outcome are not equal between two groups using the two sample proportion tests.
- 2-sided α=0.05
- Assumes 30% relative reduction in events with ***Colchicine* + Rosuvastatin** treatment

A total of 466 subjects (233 per group) will provide at least 80% power to test the primary hypothesis assuming a 44.2% event rate at 30 days in the control group, a 30% relative reduction in events with treatment, a 2-sided α=0.05 and at 10% loss to follow-up at 30 days.

11.3.2 **Powered Secondary Endpoint Analysis**

The secondary powered efficacy endpoint analysis will be a test of superiority of ***Colchicine* + Rosuvastatin** in addition to SOC compared to SOC alone assessed by the composite outcome of mechanical ventilation, myocardial injury and death measured at 30 days. The secondary endpoint will be evaluated in the ITT population. A secondary analysis will be performed in the AT population.

The sample size of 466 subjects (233 per group) will provide 85% power to test the secondary hypothesis assuming a 48% composite event rate at 30 days in the control group, a 30% relative reduction in events with treatment, a 2-sided α=0.05 and 5% loss to follow-up at 30 days.

11.3.3 **Rationale for Assumptions**

11.3.3.1 Expected Control Event Rate for Primary Endpoint

11.3.3.2 The primary endpoint event rate at 30 days was estimated using data from more recent COVID-19 studies given that improvements in SOC have reduced event rates. Per the RCT comparing dexamethasone use to placebo in COVID-19 patients from the RECOVERY trial the event rate of mechanical ventilation and death in patients not requiring mechanical ventilation at time of randomization in dexamethasone arm was **25.6%**.[43] The rates of CPAP/BiPAP/HFNC use in COVID-19 patients are not well reported but in the Remdesivir trial at 15 days **10.7%** of patients were requiring their use.[44] The true 30-day event rate will be higher given some patients will progress later and some patients would have improved by this time point. This is balanced by improvements in SOC since this trial. Per a recent meta-analysis the rate of PE and DVT in non-ICU COVID-19 patients is 10.5% and 7.4%, respectively with about 42% of patients with PE having an identified DVT.[45] This makes the composite event rate of DVT/PE approximately **14.8%**. The true incidence will likely be slightly higher given that some patients in trial will eventually be admitted to ICU and rates of DVT/PE are significantly higher in this population. Finally, the incidence of acute MI and/or ischemic stroke appears to be approximately **1%** based on a recent registry.[46] In total the sum of these event rates is 52.1%. Assuming a conservative 15% overlap in events the assumed event rate of 44.2% in the SOC arm is reasonable. Expected Control Event Rate for Secondary Powered Endpoint

The secondary powered endpoint (composite of death, myocardial injury, and invasive mechanical ventilation) event rate was estimated from data from 1,412 COVID-19 patients discharged from the Yale New Haven Health System, the system in which this trial will be undertaken. In the system the event rates for the three individual endpoints in the composite are death (17%), myocardial injury (48%), and invasive mechanical ventilation (33%). Although rates are not currently available for the composite of these three, a conservative event rate of 48% was assumed based on the highest individual event rate.

11.4 Method of Analysis and Reporting

11.4.1 General Approach

Superiority testing for the primary efficacy endpoint (Proportion of subjects that progress to severe COVID-19 disease by 30 days, as defined by the World Health Organization (WHO) Ordinal Scale for Clinical Improvement Scores 5-8) and powered secondary efficacy endpoint (Composite outcome of mechanical ventilation, myocardial injury and death measured at discharge) will be 2-sided and perfomed at 0.05 significance level. Proportions of subjects with various scores on ordinal scales (i.e. WHO ordinal scale for clinical improvement) will be compared between groups using the Chi-squared test for the ordinal logistic regression model. Analysis of all additional secondary endpoint results will be summarized using descriptive statistics. For binary variables, descriptive statistics will include counts, percentages, and sample size for each treatment group; p-values may be presented for hypothesis-generating purposes. For continuous variables, descriptive statistics include mean, median, standard deviation, quartiles, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. For time-to-event data, Kaplan-Meier estimates at the indicated time points will be displayed graphically.

Analysis will be conducted using SAS (version 9.3 or greater), unless otherwise noted. Please refer to the formal Statistical Analysis Plan (SAP) for additional details.

11.4.2 Baseline Characteristics

The following data will be summarized using descriptive statistics and presented by treatment group for the ITT and PP populations:

- Baseline demographics
- Baseline comorbidities, risk factors, medical history, and medication usage
- Baseline SOFA score

11.4.3 Primary Endpoint Analysis

The primary efficacy endpoint analysis will be a test of superiority of ***Colchicine*** + **Rosuvastatin** in addition to SOC compared to SOC alone assessed by the primary outcome of progression to severe COVID-19 disease (as defined by WHO ordinal scale scores 5-8 or 6-8 if patient at score of 5 at time of randomization) and arterial and venous thromboembolic complications at 30 days. The primary endpoint will be evaluated in the ITT population. A secondary analysis will be performed in the AT population. An additional analysis will be performed in the mAT population.

11.4.4 Secondary Powered Endpoint

The secondary powered endpoint analysis will be a test of superiority of ***Colchicine*** + **Rosuvastatin** in addition to SOC compared to SOC alone assessed by the composite outcome of mechanical ventilation, myocardial injury and death measured at 30 days. The secondary endpoint will be evaluated in the ITT population. A secondary analysis will be performed in the AT population. An additional analysis will be performed in mAT population.

11.4.5 **Secondary Endpoints**

All secondary endpoints will be evaluated in the ITT population using appropriate descriptive statistics at 30 and 60 day timepoints. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. Proportions of subjects with various scores on ordinal scales (i.e. WHO ordinal scale for clinical improvement) will be compared between groups using the Chi-squared test for the ordinal logistic regression model (null hypothesis states that the slope coefficients in the model are the same across response categories). An additional analysis will be performed in mAT population.

11.4.6 **Secondary Imaging Endpoint**

Secondary imaging endpoint will be performed in a subset of 50 subjects with documented myocarditis at 30 days after discharge by MRI. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group.

11.4.7 **Subgroup Analyses**

Subgroup analyses will be performed for all primary and secondary endpoints for the following subgroups:

- Subject age (<65 years vs. ≥65 years)
- Subject gender (males vs. females)
- Presence of diabetes
- Presence of hypertension
- Presence of CAD
- Presence of high-risk factors including CAD, HTN, cerebrovascular disease, CKD, heart failure.
- Subjects naive to colchicine/statins prior to admission
- Subjects receiving other medications as part of SOC or other experimental trial (including antiplatelet agents, ACEi/ARB, Remdesivir, tocilizumab, interferon-beta, and/or methylprednisolone)
- SOFA score tertiles on randomization
- WHO score on randomization
- Center of enrollment

11.5 Measure to Minimize Bias

11.5.1 **Randomization**

All COVID 19 + patients identified at YNHH and health system through EPIC will be screened for enrollment and randomized to SOC or SOC in addition to Rosuvastatin and Colchicine using an EPIC based randomization tool.

11.5.2 **Blinding**

The COLSTAT trail is an open-label trial. The Clinical Event Committee will be blinded to treatment allocation.

11.5.3 **Independent Assessments**

An independent DSMB will oversee the safe and ethical conduct of the trial. The DSMB will have the authority to discontinue the trial on the basis of safety concerns.

11.5.4 **Publication Policy**

The Yale University and the Principal Investigators are committed to the publication and widespread dissemination of the results of the study in the scientific community.

12.0 Data Collection and Monitoring

12.1 Data Collection and Monitoring

Block randomization will be performed through the electronic medical records (EPIC) and will be linked to and order set for colchicine and rosuvastatin. All data testing, blood samples, and point of care echocardiography are within the current standard of care algorithm and no additional data collection beyond standard of care is required. Data will be exported using a Joint Data Analytics Team (JDAT) export from EPIC enabling a system wide implementation of the trial. Data will be monitored for completeness and accuracy.

12.2 Source Documentation

Auditors, monitors, the Yale University IRB, and other regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled patient (no source documentation will be recorded directly on the CRF). At a minimum, the following must be included in each patient's file:

- Sufficient medical history and current physical condition, including any medication(s) the patient is taking at the time of the procedure to assess the patient's eligibility;
- The medical file should reveal the patient's participation in this study, including documentation of informed consent;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of patient consent, the reason and patient status at time of withdrawal.

The Principal Investigator will permit study-related monitoring, audits, IRB review, and other applicable regulatory authority inspections by allowing direct access to the source data.

In case of electronic source data, periodic access will be allowed for full safety review. The review will be specific to study subjects and the records that would contain potential safety data. Dated printouts are acceptable for preliminary review of safety information. Print-outs should include all available data related to the identified patient(s).

12.3 Auditing

As a quality assurance measure, investigational sites may be audited during the trial or following trial completion. The purpose of an audit is to provide an independent evaluation of trial conduct and protocol and GCP compliance, separate from routine monitoring and quality control functions. The audit may be conducted by the Yale University personnel (or designee), or another regulatory body.

The Principal Investigator shall permit the Yale University and regulatory bodies direct access to source data and all other relevant documents.

13.0 Ethical and Regulatory Considerations

13.1 Applicable Regulations

This trial will be conducted in compliance with this protocol, the Yale University's standard operating procedures and/or guidelines, FDA regulation, ICH GCP guidelines and, the Declaration of Helsinki.

13.2 Institutional Review Board

This trial will be conducted in accordance with Yale Institutional Review Boards. Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the IRB and written approval obtained prior to implementation.

Substantive changes will be submitted to the Yale IRB prior to implementation, and local regulatory authorities, as applicable, will be notified of any changes not requiring approval according to applicable guidelines.

13.3 Insurance

The Yale University will maintain clinical trial insurance coverage for the duration of the study in accordance with applicable local laws and regulations. Details of insurance, indemnity, compensation, and reimbursement shall be addressed in a separate agreement approved by the interested parties.

13.4 Regulatory Approval

The Yale University is responsible for notifying the study to any relevant authorities (as applicable) according to regulatory requirements. Investigators may not commence enrollment of subjects until they have met any local IRB and hospital management requirements and have received confirmation from the Yale University that the appropriate regulatory approvals have been obtained.

13.5 Trial Registration

This trial meets the definition of an “applicable clinical trial” according to Section 801 of the Food and Drug Administration Amendments Act. The Yale University affirms that it will serve as the Responsible Party and fulfill all requirements regarding trial registration, the provision of clinical trial information, and results reporting through the ClinicalTrials.gov registry data bank.

Clinical trial information will be submitted no more than 21 days after the first subject is enrolled in the trial, and results information will be submitted no later than 1 year after completion of the trial.

13.6 Records and Reports

The Yale University and Principal Investigator will maintain records related to this study for 7 years (or longer according to local requirements) after the end of this study.

Records will include:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- *Curriculum vitae*
- Adverse event information
- Complaint documentation
- All data forms prepared and signed by the Investigators and all received source documentation and core laboratory reports
- Clinical Investigation Plan (CIP) and any amendments
- Site monitoring reports
- Financial disclosure information

The Yale University and Principal Investigator are each responsible for the preparation, review, and submission of all required reports in accordance with local laws and regulations, the requirements of the FDA and other regulatory authorities as applicable, and the requirements of the Yale IRB.

13.7 Protocol Amendments

Any protocol amendments will be approved by the Yale University, the Principal Investigators, the IRB and any necessary regulatory body before it can be implemented. Substantive changes will be submitted to regulatory authorities as applicable for approval prior to implementation, and regulatory authorities as applicable will be notified of any changes not requiring approval in accordance with relevant guidelines.

13.8 Informed Consent

Informed consent will be obtained and documented as described §6.4 prior to the performance of any study-specific procedures or assessments in accordance with applicable laws and regulations, and local IRB requirements.

Subjects will not be compensated.

13.9 Termination of the Study

The Yale University reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Possible reasons for early trial termination include:

- Unanticipated Adverse Effects present an unreasonable risk to patients
- Recommendation from the DSMB

Data will be reviewed based on JDAT exports at the same intervals defined for the DSMB. If a determination to discontinue the trial is recommended by the DSMB, the IRB will be notified within 5 days. Study investigators in the health system will be notified and the randomization through EPIC disabled.

The Yale University will also inform the FDA when required. In the case of early termination of trial enrollment, follow-up visits will continue for all enrolled subjects.

13.10 Patient Privacy

The Yale University affirms and upholds the principle of patient confidentiality. Throughout this study, all data provided will only be identified by a study-specific subject identification number. “Protected Health Information” will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and applicable local regulations.

The Principal Investigator agrees that representatives of the Yale University, its designee(s), and regulatory authorities may inspect included patients’ records to verify trial data, provide the data are treated as confidential and that the subject’s privacy is maintained.

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15.0 Appendices

15.1 Appendix A: Definitions

Acute Kidney Injury (AKI) [AKIN classification]

Change in serum creatinine (up to 7 days) compared with baseline[48]:

- **Stage 1:**
  - Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR
  - Urine output <0.5 ml/kg per hour for >6 but <12 hours
- **Stage 2**:
  - Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR
  - Urine output <0.5 ml/kg per hour for >12 but <24 hours
- **Stage 3**:
  - Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR
  - Urine output <0.3 ml/kg per hour for ≥24 hours OR
  - Anuria for >12 hours
  - [Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria]

Acute Limb Ischemia

A rapid or sudden decrease in limb perfusion plus either 1) a new pulse deficit, rest pain, pallor, paresthesia, or paralysis; or 2) confirmation of arterial obstruction by limb hemodynamics (ankle or toe pressure), imaging, intraoperative findings, or pathological evaluation. Events will be classified per the Rutherford Classification[49]

Adverse Events

According to 21CFR312.32:

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event could present as an abnormal laboratory finding, abnormal imaging finding or an abnormal clinical finding or symptom.

Life-threatening adverse event or life-threatening suspected adverse reaction

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event *or* serious suspected adverse reaction

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event *or* unexpected suspected adverse reaction.

	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.
As Treated (AT) Population	As Treated (AT) analysis population is defined by the treatment actually received, rather than the treatment assigned. The mAT analysis population is defined by the treatment actually received, rather than the treatment assigned and excludes all subjects with prior statin therapy.
Bleeding	Defined according to the following BARC definitions[50]: • **Type 0**: no bleeding • **Type 1**: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional • **Type 2**: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation • **Type 3** Type 3a Over bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with over bleeding Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed comprising vision

- **Type 4**: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period (NOTE: cell saver products are not counted)

Chest tube output ≥2L within a 24-h period

- **Type 5**: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

NOTES:

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin)

Childs-Pugh Class

Points	+1	+2	+3
Encephalopathy*	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
PT (sec prolonged) or INR	< 4 < 1.7	4-6 1.7-2.3	> 6 > 2.3

Child-Pugh Class:

A = 5-6 points
B = 7-9 points
C = 10-15 points

*Encephalopathy Grade

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Death

Classified as cardiac, vascular, or noncardiovascular according to the following ARC definitions.[51] All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer, infection) should be classified as cardiac.

- Cardiac death: Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-

related deaths, including those related to concomitant treatment, will be classified as cardiac death.

- Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.
- Non-cardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Glasgow Coma Scale

The Glasgow coma scale is a score between 3-15 assessed as the sum of three categories:

- Eye Response
    1. No eye opening
    2. Eye opening to pain
    3. Eye opening to verbal command
    4. Eyes open spontaneously
- Motor Response
    1. No motor response
    2. Extension response to pain
    3. Flexion response to pain
    4. Withdraws from pain
    5. Localizes to pain
    6. Obeys commands
- Verbal Response
    1. No verbal response
    2. Incomprehensible sounds
    3. Inappropriate words
    4. Confused
    5. Oriented

High Flow Nasal Cannula/High Flow Oxygen

Delivery of warmed and humidified oxygen at high flows through nasal cannula typically at rates of 5-60L/min

Intention to Treat (ITT) Population

All subjects enrolled in the study, analyzed by assigned treatment, regardless of the treatment actually received.

Invasive Mechanical Ventilation	Assisted ventilation with endotracheal tube or tracheostomy tube
Mortality	See “death”
Myocardial infarction (MI)	The primary protocol definition of myocardial infarction is the Fourth Universal Definition[52] provided in the Table below, which will be adjudicated and classified by an independent CEC. When quantitative troponin is not available CK-MB will be used in its place In addition, the CEC will also adjudicate PCI-related MI according to several alternate thresholds of cTn (3, 10, 35, and 70 × 99th percentile URL), and all MI types (except Type 3) will be tabulated according to multiples of the 99th percentile URL of cTn as recommended by Thygesen et al.[53]

Definition of Myocardial Infarction[52,53]
Criteria for myocardial injury The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.
Criteria for acute myocardial infarction (types 1, 2, and 3 MI)
The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: • Symptoms of myocardial ischaemia; • New ischaemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; • Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs). Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.
Criteria for coronary procedure-related myocardial infarction (types 4 and 5)
Percutaneous coronary intervention (PCI) related MI is termed type 4a MI. Coronary artery bypass grafting (CABG) related MI is termed type 5 MI.

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to type 4a MI only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria.

Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/ unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

Clinical criteria

Clinical criteria for MI

The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.

Clinical criteria for myocardial injury

Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following: Symptoms of acute myocardial ischaemia; New ischaemic ECG changes; Development of pathological Q waves; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[a]

Criteria for type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

Criteria for type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Criteria for cardiac procedural myocardial injury

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (> 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% of the baseline value when it is above the 99th percentile URL but it is stable or falling

Criteria for PCI-related MI ≤48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[b]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.[c]

Criteria for CABG-related MI ≤ 48 h after the index procedure (type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;[d]
- Angiographic documented new graft occlusion or new native coronary artery occlusion;

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology.

Criteria for prior or silent/unrecognized MI

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Pathological Q waves, with or without symptoms, in the absence of nonischaemic causes;
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology;
- Pathological findings of a prior MI.

Electrocardiographic manifestations suggestive of acute myocardial ischaemia (in the absence of left ventricular hypertrophy and bundle branch block)

ST-elevation

New ST-elevation at the J-point in two contiguous leads with the cutpoint: ≥ 1 mm in all leads other than leads V_2–V_3 where the following cut-points apply: ≥ 2mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age.[e]

ST-depression and T wave changes

New horizontal or downsloping ST-depression ≥ 0.5 mm in two contiguous leads and/or T inversion > 1 mm in two contiguous leads with prominent R wave or R/S ratio > 1.

Electrocardiographic changes associated with prior myocardial infarction (in the absence of left ventricular hypertrophy and left bundle branch block)

Any Q wave in leads V_2–V_3 > 0.02 s or QS complex in leads V_2–V_3.

Q wave ≥ 0.03 s and ≥ 1 mm deep or QS complex in leads I, II, aVL, aVF or V_4–V_6 in any two leads of a contiguous lead grouping (I, aVL; V_1–V_6; II, III, aVF).[f]

R wave > 0.04 s in V_1–V_2 and R/S > 1 with a concordant positive T wave in absence of conduction defect.

*If cTn is not available, CKMB (measured by mass assay) is an acceptable alternative. The CKMB threshold for the diagnosis of PCI-related MI is >5 × 99th percentile URL in patients with normal baseline values.

CABG = coronary artery bypass grafting; cTn = cardiac troponin; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention; URL = upper reference limit.

[a]Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.

[b]Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but more than five times the 99th percentile URL.

[c]Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

[d]Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.

[e]When the magnitudes of J-point elevation in leads V_2 and V_3 are registered from a prior electrocardiogram, new J-point elevation ≥ 1 mm (as compared with the earlier electrocardiogram) should be considered an ischaemic response.

[f]The same criteria are used for supplemental leads V_7–V_9. s = seconds

Myocarditis

Based on the scientific statement from the American Heart Association[54]:

Clinical presentations*

Acute chest pain, pericarditic, or pseudoischemic

New onset (days up to 3 mo) or worsening of dyspnea at rest or exercise, and/or fatigue, with or without signs of left- and/or right-sided heart failure

Subacute/chronic (>3 mo) or worsening of dyspnea at rest or exercise, and or fatigue with or without left- and/or right-sided heart failure

Palpitation and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death

Unexplained cardiogenic shock

Diagnostic criteria

I. ECG/Holter/stress test features

New abnormal 12-lead ECG and/or Holter stress testing, any of the following: first- to third-degree atrioventricular block or bundle-branch block; ST/T-wave changes; sinus arrest; ventricular tachycardia or fibrillation and asystole; atrial fibrillation; reduced R-wave height; intraventricular conduction delay (widened QRS complex); abnormal Q waves; low-voltage, frequent premature beats; supraventricular tachycardia

II. Myocardiocytolysis markers

Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echocardiogram/angiography/CMR)

New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall

thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

Edema and/or LGE of classic myocarditic pattern (see Role of Cardiac MRI in Suspected Myocarditis)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories in the absence of (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%) or (2) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, hyperthyroidism). Suspicion is higher with higher number of fulfilled criteria. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TnI, troponin I; and TnT, troponin T.

*If the patient is asymptomatic, ≥2 diagnostic criteria should be met.

Myopathy[55]

- Complaints of myalgia (muscle pain or soreness), weakness, and/or cramps, plus
- Elevation in serum CK >10× the ULN
- A patient may describe intolerable muscle symptoms but not be found to have a CK level >10 times the ULN. This patient may be considered to be experiencing myopathy for the purposes of further evaluation.

Noninvasive Ventilation

Assisted ventilation using mouth, nasal, and/or face mask such as bilevel positive airway pressure (BiPAP) or continuous positive airway pressure [CPAP]. Does not include nasal cannula or high flow oxygen

Overt Disseminated Intravascular Coagulation (DIC)[56]

Variable		Points
Platelet count, cells x 10^9/L	≥100	+0
	50 to <100	+1
	<50	+2
Elevated levels of a fibrin-related marker* (e.g. D-dimer, fibrin degradation products)	No increase	+0
	Moderate increase	+2
	Severe increase	+3
Prolonged PT, seconds	<3	+0
	3 to <6	+1
	≥6	+2
Fibrinogen level, g/L	≥1	+0

	<1	+1

* Use lab-specific cutoff values

Score:

< 5: Not suggestive of overt DIC, may be non-overt DIC; repeat within next 1-2 days and manage clinically as appropriate

> 5: Compatible with overt DIC; treat for DIC as appropriate and repeat scoring daily

Pulmonary Embolism (PE)

Pulmonary embolism is a mechanical obstruction of one or more branches of the pulmonary vasculature, usually from a clot.

These must be diagnosed by objective image such as computed tomography angiography and will be stratified based on following criteria:

- Massive or high-risk: the PE is causing hemodynamic instability.
- Submassive or intermediate risk: the PE is causing cardiac dysfunction with right ventricular strain (echocardiographic findings may include right ventricular hypokinesis or dilation, tricuspid regurgitation, and/or paradoxic septal movement), frequently with elevations in troponin and/or brain natriuretic peptide (BNP).
- Low risk: absence of any signs of massive or submassive PE.

QTc prolongation (Per YNHH COVID-19 protocol)

QTc > 470 ms and narrow QRS (<120 ms) OR QTc > 500 ms and wide QRS (>120 ms)

OR if already abnormal on enrollment an increase by 50ms

Rhabdomyolysis[55]

- CK >10,000 IU/L, or
- CK >10× the ULN plus an elevation in serum creatinine or medical intervention with IV hydration therapy (the CK level may be <10 times the ULN depending on the temporal relation between the event and the drawing of the laboratory sample)

Sequential Organ Failure Assessment (SOFA) score

Score based on organ dysfunction that predicts ICU mortality. Scored in six categories with scores of 0-24 possible:

PaO2/FiO2

≥400	0
300-399	+1

200-299	+2
100-199 and mechanically ventilated	+3
<100 and mechanically ventilated	+4

Ok to replace use SpO2/FiO2 ratio when ABG not available using the following criteria[2]:

SOFA Respiratory score	PaO_2/FiO_2	SpO_2/FiO_2
1	<400	<512
2	<300	<357
3	<200	<214
4	<100	<89

Platelets x 1000

≥150	0
100-149	+1
50-99	+2
20-49	+3
<20	+4

Glasgow Coma Scale

15	0
13–14	+1
10–12	+2
6–9	+3
<6	+4

Bilirubin (mg/dL)

<1.2 (<20)	0
1.2–1.9 (20-32)	+1
2.0–5.9 (33-101)	+2
6.0–11.9 (102-204)	+3
≥12.0 (>204)	+4

Mean arterial pressure OR administration of vasoactive agents required (listed doses are in units of mcg/kg/min)

No hypotension	0
MAP <70 mmHg	+1
DOPamine ≤5 or DOBUTamine (any dose)	+2
DOPamine >5, EPINEPHrine ≤0.1, or norEPINEPHrine ≤0.1	+3
DOPamine >15, EPINEPHrine >0.1, or norEPINEPHrine >0.1	+4

Creatinine (mg/dL)

<1.2 (<110)	0

1.2–1.9 (110-170)	+1
2.0–3.4 (171-299)	+2
3.5–4.9 (300-440) or UOP <500 mL/day)	+3
≥5.0 (>440) or UOP <200 mL/day	+4

Severe QTc Prolongation (Per YNHH COVID-19 protocol)

QTc > 500 ms with narrow QRS (<120 ms) OR QTc > 550 ms with wide QRS (>120 ms)

Stroke [48]

Diagnostic criteria:

Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death

TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct

No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist

Confirmation of the diagnosis by at least one of the following

Neurologist or neurosurgical specialist

Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification

Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue

Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

According to the **NeuroARC definition**[57]:

Overt CNS Injury: Acutely symptomatic brain or spinal cord injury (NeuroARC Type 1) including:

Type 1.a Ischemic stroke

Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

1) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either:
   a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or*
   b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected

   or

2) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 1.b Symptomatic intracerebral hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma

Type 1.c Symptomatic subarachnoid hemorrhage

	Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma Type 1.d Stroke, not otherwise specified An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified as either (i.e., no neuroimaging performed) Type 1.e Symptomatic hypoxic-ischemic injury Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia **Covert CNS Injury:** Acutely symptomatic brain or spinal cord injury detected by neuroimaging (NeuroARC Type 2) including: Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location Subtype 2.a.H Covert CNS infarction with hemorrhagic conversion Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion. Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect Type 2.b Covert CNS hemorrhage Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location
Systemic Thromboembolism	Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation).[58] When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.

Thromboembolism may be arterial or venous in nature and involves the obstruction, partial or total occlusion, of a part of the circulatory system and may detected by a variety of imaging modalities including angiography, venography, computed tomography, radiography and other or may be detected on autopsy.

Thrombosis

Local coagulation or clotting of the blood in a part of the circulatory system. Thrombosis in the central nervous system or brain parenchyma should be evaluated for the occurrence of an ischemic stroke.

Venous Thrombosis

Venous thrombosis is defined as a blood clot forming in venous system, most often in the deep veins of the leg, groin or arm (i.e. deep vein thrombosis).

For purposes of this trial this must be diagnosed with objective imaging such as ultrasound, computed tomography, or angiography

WHO Ordinal Scale for Clinical Improvement[59]

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

15.2 Appendix B: List of Abbreviation

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
ACEi	Angiotensin Converting Enzyme inhibitor
ACE2	Angiotensin Converting Enzyme 2
ACS	Acute Coronary Syndromes
AKI	Acute Kidney Injury
ALI	Acute Lung Injury
ARB	Angiotensin II Receptor Blocker
ARC	Academic Research Consortium
ARDS	Acute Respiratory Distress Syndrome
AT	As Treated
BARC	Bleeding Academic Research Consortium
BiPAP	Bilevel Positive Airway Pressure
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CCL5	C-C Chemokine Ligand 5
CCS	Canadian Cardiovascular Society (grading scale of angina pectoris)
CEC	Clinical Events Committee
CI	Confidence Interval
CIP	Clinical Investigation Plan
CK	Creatine Kinase
CKMB	Creatine Kinase MB isoform

CMP	Complete Metabolic Panel
COLCOT	Colchicine Cardiovascular Outcomes Trial
COVID-19	Coronavirus Disease of 2019
CP	Conditional Power
CPAP	Continuous Positive Airway Pressure
CPK	Creatine Phospokinase
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
cTn	Cardiac Troponin
CXR	Chest X-Ray
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture (system)
eGFR	Estimated Glomerular Filtration Rate
FDA	U.S. Food and Drug Administration
FiO2	Fraction of inspired Oxygen
GCP	Good Clinical Practices
GFR	Glomerular Filtration Rate
HFNC	High Flow Nasal Cannula
HIPAA	Health Insurance Portability and Accountability Act of 1996
H&P	History and Physical

HR	Hazard Ratio
hsCRP	High Sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IFG	Interferon Gamma
IL	Interleukin
IL-2R	Interleukin 2 Receptor
IP-10	Inducible Protein 10
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention To Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
JDAT	Joint Data Analytics Team
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LoDoCo	Low-Dose Colchicine trial
LVEF	Left Ventricular Ejection Fraction
MERS	Middle East Respiratory Syndrome
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
PaO2	Partial Pressure of Oxygen
PCI	Percutaneous Coronary Intervention

PE	Pulmonary Embolism
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RCT	Randomized Controlled Trial
RT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	Standard of Care
SOFA Score	Sequential Organ Failure Assessment Score
SpO2	Oxygen Saturation
STEMI	ST-Segment Elevation Myocardial Infarction
TBD	To Be Determined
TEAE	Treatment Emergent Adverse Events
TG	Triglyceride
TNF-α	Tumor Necrosis Factor Alpha
ULN	Upper Limit Normal
URL	Upper Reference Limit
VARC-2	Valve Academic Research Consortium-2
WHO	World Health Organization