Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Design and rationale of the colchicine/statin for the prevention of COVID-19 complications (COLSTAT) trial

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ABSTRACT

Background: Despite improvement in the standard of care (SOC) for hospitalized COVID-19 patients, rates of morbidity and mortality remain high. There continues to be a need for easily available and cost-effective treatments. Colchicine and rosuvastatin are both safe and well-studied medications with anti-inflammatory and other pleiotropic effects that may provide additional benefits to hospitalized COVID-19 patients.

Methods and results: The Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) trial is a pragmatic, open-label, multicenter, randomized trial comparing the combination of colchicine and rosuvastatin in addition to SOC to SOC alone in hospitalized COVID-19 patients. Four centers in the Yale New Haven Health network will enroll a total of 466 patients with 1:1 randomization. The trial will utilize the electronic health record (Epic® Systems, Verona, Wisconsin, USA) at all stages including screening, randomization, intervention, event ascertainment, and follow-up. The primary endpoint is the 30-day composite of progression to severe COVID-19 disease as defined by the World Health Organization ordinal scale of clinical improvement and arterial/venous thromboembolic events. The secondary powered endpoint is the 30-day composite of death, respiratory failure requiring intubation, and myocardial injury.

Conclusions: The COLSTAT trial will provide evidence on the efficacy of repurposing colchicine and rosuvastatin for the treatment of hospitalized COVID-19 patients. Moreover, it is designed to be a pragmatic trial that will demonstrate the power of using electronic health records to improve efficiency and enrollment in clinical trials in an adapting landscape.

Clinical Trial Registration: NCT04472611 (https://clinicaltrials.gov/ct2/show/NCT04472611).

1. Introduction

The COVID-19 pandemic caused by the viral pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 200 million people and resulted in 4 million deaths worldwide. SARS-CoV-2 causes severe disease through direct viral invasion, hyperinflammatory host responses, and micro/macro-thrombotic reactions [1–9]. Thus far, for hospitalized patients, 3 treatments have shown benefit in randomized clinical trials (RCTs) and have been adopted as standard of care (SOC): the antiviral remdesivir [10] and the anti-inflammatory medications dexamethasone and tocilizumab [11–14]. Despite this, mortality in treated hospitalized patients in these trials remains up to 30%, and there is an imperative to identify further treatment strategies to improve outcomes. To this end, colchicine and statins are well studied and readily available medications with anti-inflammatory effects that may provide additional benefit in patients

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with COVID-19 based on available evidence [15–22]. We hypothesized that the combination of rosuvastatin and colchicine, which has been used safely in cardiac patients [23,24], may reduce the severity of COVID-19 disease in infected patients.

2. Trial design and methods

The Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) trial is a pragmatic, open-label, multicenter, randomized trial comparing the combination of colchicine and rosuvastatin in addition to SOC to SOC alone in patients hospitalized for acute SARS-CoV-2 infection (Fig. 1). The trial will be conducted in the Yale New Haven Health (YNHH) network of hospitals in Connecticut (Bridgeport Hospital, Greenwich Hospital, Lawrence & Memorial Hospital, and Yale New Haven Hospital). SOC is defined by the YNHH consensus treatment algorithm for COVID-19 patients. The study was reviewed by the Food and Drug Administration and deemed exempt from investigational new drug application (IND), was approved by Yale Institutional Review Board (IRB), and registered with ClinicalTrials.gov (NCT04472611).

2.1. Patient selection and consent

The major inclusion criteria for this study are any patients 18 years or older with SARS-CoV-2 infection requiring admission to a non-intensive care unit (ICU) within 72 h of randomization and able to provide informed consent. Major exclusion criteria include patients requiring ICU level care before randomization as defined by World Health Organization (WHO) disease severity scale ≥6 (Table 1) [17], pregnant or nursing mothers, chronic colchicine therapy, known allergies to statins or colchicine, elevated transaminases, severely reduced glomerular filtration rate (GFR <30 mL/min), severe QTc prolongation, rhabdomyolysis based on creatine kinase (CK) elevation, or severe thrombocytopenia/leukopenia/anemia (Table 2). Prior statin use is not an exclusion criterion in this study, as it would exclude a large quantity of patients, particularly those at highest risk for severe disease.

Table 1
WHO ordinal scale of clinical improvement.

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

ECMO: extracorporeal membrane oxygenation, RRT: renal replacement therapy.

2.2. Utilization of electronic health record (EHR) system

The methodology of the COLSTAT trial is unique in that it is one of the first trials to fully utilize the EHR (Epic® Systems, Verona, Wisconsin, USA) at all stages of the clinical trial including screening, randomization, intervention, and follow-up. It is designed to enable more efficient screening, enrollment, and follow-up of patients across multiple centers within the YNHH network. Epic® is programmed to identify any adult COVID-19 positive patients admitted to a non-ICU bed at any of the 4 YNHH network hospitals who do not have any severe cytopenias, as defined by the exclusion criteria. Prior consented or declined patients are excluded as well. Eligible patients are electronically "pushed" to the Epic® in-baskets of approved research coordinators to complete a manual screening of patients' charts for eligibility in the trial (Fig. 2). Criteria including transaminases, GFR, and CK, which may change rapidly over the course of 72 h, were not used in automated screening to avoid inappropriate inclusion or exclusion of patients. Once patients are deemed eligible, they or their legal decision-maker are approached in person or by phone. The protocol allows for in-person or over-the-phone consenting that is witnessed by at least 2 healthcare providers and is documented in Epic®. Consent status is further incorporated in the screening logic to exclude patients from re-inclusion.

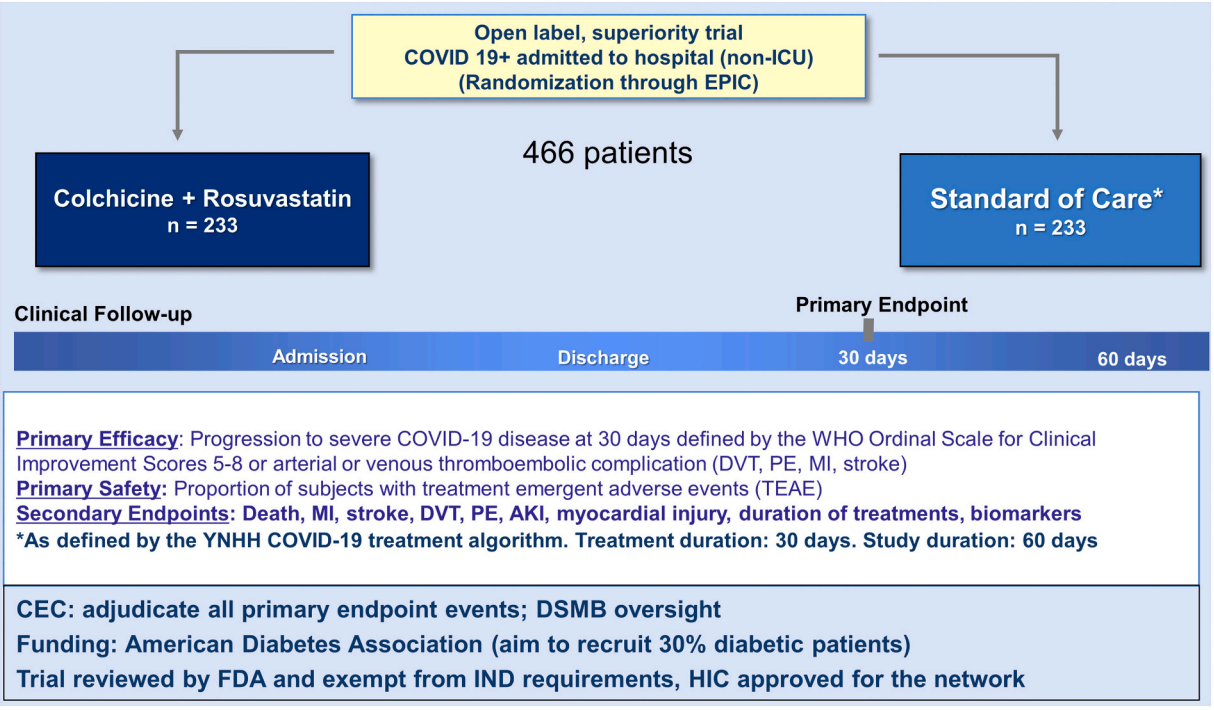

Fig. 1. Trial design.

Table 2
Inclusion/Exclusion Criteria.

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 h of hospital admission (WHO ordinal scale of clinical improvement 3–5) 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
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 >3× ULN) 5. Severe chronic kidney disease defined as glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 6. Severe QTc prolongation (>500 ms narrow QRS <120 ms and > 550 ms for wide QRS ≥120 ms) 7. Presents with severe disease on admission requiring ICU admission (WHO ordinal scale of clinical improvement scores 6–8) 8. Rhabdomyolysis or CPK >5× ULN 9. Thrombocytopenia defined as platelet count <50,000/mm^3 10. Leukopenia defined as white blood cell count <2500/μL 11. Severe anemia defined as hemoglobin value <8 g/100 mL 12. Participation in any other clinical trial of an experimental treatment for COVID-19

2.3. Randomization

After obtaining and documenting informed consent associated with the study in Epic®, a randomization module restricted to IRB-approved providers (principal investigator or delegate listed on the study record) is triggered upon opening the patient's chart. The randomization best practice advisory (BPA) evaluates for presence of study-associated consent and appropriate clinician and uses simple randomization in a 1:1 ratio within the Epic EHR using an internal random number generator. Block randomization is not yet available through the Epic EHR. If the patient is assigned to the active arm (colchicine and rosuvastatin in addition to SOC) the BPA presents an order set with colchicine and rosuvastatin defaulted in addition to displaying the patients' relevant laboratory values, including GFR and liver function tests, that would trigger protocol-defined dose reductions (Fig. 2). A research progress note using an EHR macro (Epic® smart phrase) is left in each patient's chart to detail the informed consent process, the rationale of the trial, and potential adverse events to inform the in-hospital treatment teams.

2.4. Intervention

When patients are randomized to the active arm, they receive rosuvastatin and colchicine for the duration of the hospitalization or 30 days, whichever is shorter. All other care, including labs, imaging, and other interventions are according to the approved YNHH COVID-19 treatment algorithm. All patients in the active arm will receive high-intensity rosuvastatin 40 mg daily and a loading dose of colchicine for the first 3 days (0.6 mg twice daily) and then continue the maintenance dose (0.6 mg daily). Treatment will continue for the duration of the hospitalization until 30 days or discharge, whichever comes first. If a patient was on a statin prior to hospitalization, it will be switched to rosuvastatin 40 mg (highest intensity statin available) and then switched back to the home medication at hospital discharge. For safety, doses of colchicine will be adjusted for concurrent use of CYP3A4 inhibitors or protease inhibitors, and doses for both colchicine and rosuvastatin will be adjusted for GFR <30 mL/min. Study drugs 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 serious adverse event or ≥ Grade 3 adverse event is suspected to be related to treatment, any elevation of ALT >5× the upper limit of normal (ULN) confirmed by repeat testing, any elevation of CK >5× ULN confirmed by repeat testing or severe myalgias suspected related to statin therapy. Additionally, any subjects who develop renal or hepatic impairment and require a protease inhibitor or strong CYP3A4 inhibitor should discontinue colchicine, and subjects who develop new blood dyscrasia including leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia should also discontinue colchicine. All protocol-defined adverse events are "pushed" to the EPIC in-basket of the principal investigators and coordinator regardless of randomized allocation. In addition, the adjudication of all clinician-reported adverse events, regardless of treatment, will be reviewed independently, blinded to treatment allocation.

2.5. Follow-up

After discharge if a patient returns to the Emergency Department, is admitted to any YNHH network hospital, or is marked as deceased in Epic, their chart is routed to the Epic research coordinators' in-baskets for further follow-up and adverse event reporting. In addition, all patients will be contacted at 30 days and 60 days after randomization for telephone follow-up.

2.6. Endpoints

The primary endpoint in the COLSTAT study is the proportion of subjects who progress to severe COVID-19 disease by 30 days as defined by the WHO Ordinal Scale for Clinical Improvement Scores 5–8 (or 6–8 if patient is at score of 5 at time of randomization) or develop arterial or venous thromboembolic complications confirmed by imaging (including deep venous thrombosis, myocardial infarction, and ischemic stroke) (Table 3). Myocardial infarction (MI) is defined using the Fourth Universal Definition of MI [25] and ischemic stroke is defined by the NeuroARC definition [26]. A secondary powered endpoint is defined as the composite of respiratory failure requiring mechanical ventilation, any myocardial injury, or death at 30 days. Myocardial injury is defined as a troponin >99th percentile of the upper reference limit, a ≥ 2-fold increase if troponin is abnormal at baseline, or a new >10% reduction in left ventricular ejection fraction by echocardiography. Myocardial injury is included in this secondary endpoint, as it was associated with markedly worse outcomes in COVID-19 patients [6], and colchicine and statins are known to have cardioprotective effects [23,24]. Other secondary endpoints, including various clinical and biomarker endpoints, are detailed in Table 3.

2.7. Statistical considerations

The primary endpoint event rate at 30 days was estimated using data from the most recent COVID-19 studies at the time given that improvements in SOC have reduced event rates. These trials have similarly unrestrictive enrollment criteria in order to enroll most COVID-19 patients requiring hospitalization. Although these trials allowed enrollment of mechanically ventilated patients, they were not included in the assumed event rates below. From the RECOVERY trial comparing dexamethasone use to placebo in COVID-19 patients, the 28-day event rate of mechanical ventilation and death in patients not requiring mechanical ventilation at time of randomization in the dexamethasone arm was 25.6% [29]. The rates of continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and high flow nasal cannula (HFNC) use in COVID-19 patients not initially requiring them were not well reported at the onset of this trial, but in the remdesivir

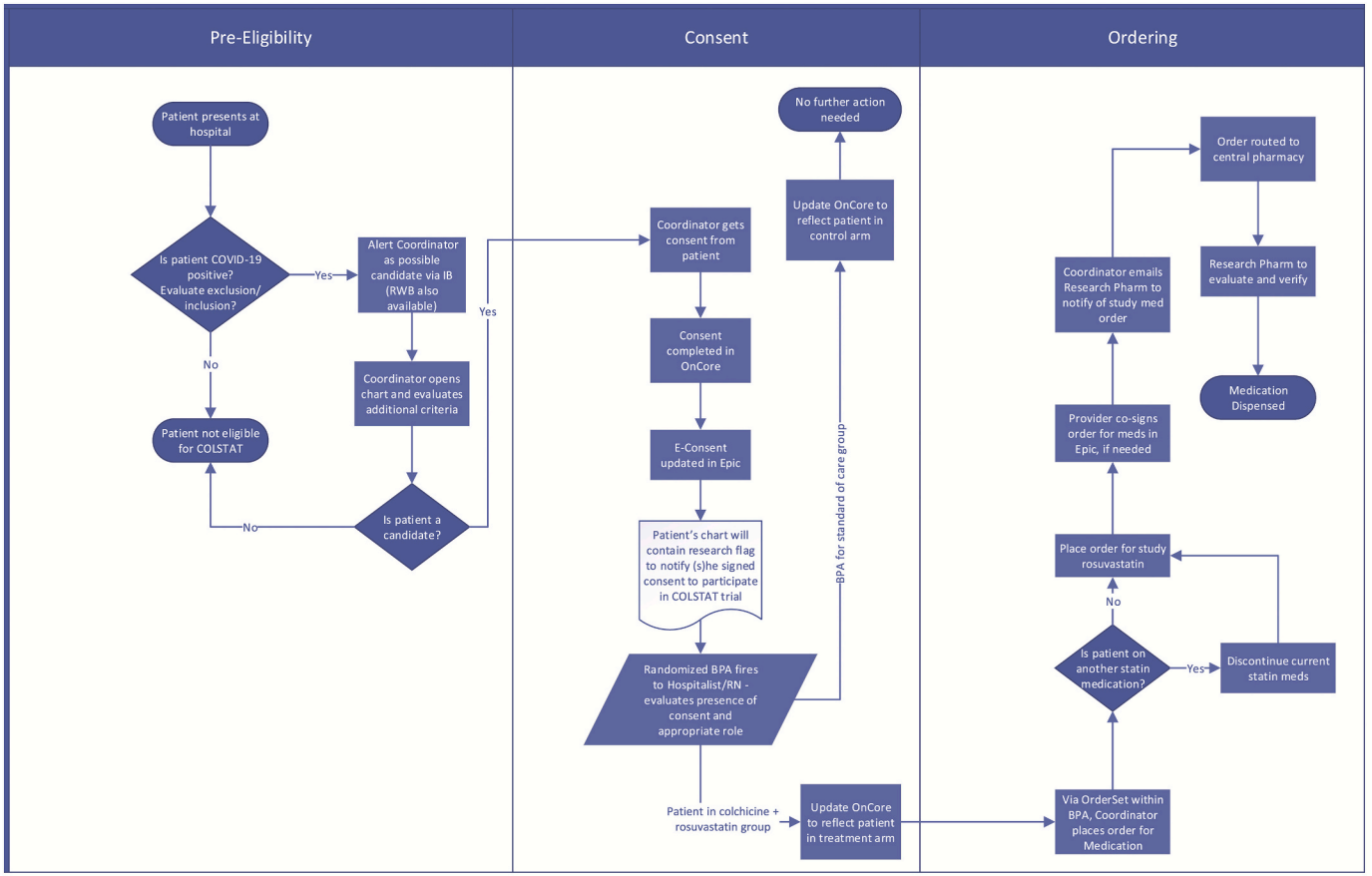

Fig. 2. COLSTAT Trial Workflow. BPA = best practice advisory; IB = in-basket; RWB = reporting workbench.

Table 3
Trial endpoints.

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).
Powered Secondary Efficacy Endpoint	Secondary Powered Efficacy Endpoint assessed at 30 days defined as a composite of 1. Respiratory failure requiring invasive mechanical ventilation, 2. Any myocardial injury (troponin URL >99th percentile or a ≥ 2-fold increase if troponin is abnormal at baseline, or a new >10% reduction in LVEF by echocardiography) 3. Death
Secondary Endpoints	Secondary endpoints will be reported by treatment group at 30 and 60 days: Clinical Safety and Efficacy: 1. Death (all-cause and cardiovascular) 2. Duration of oxygen therapy (days) 3. Duration of invasive mechanical ventilation (days) 4. Duration of intensive care treatment (days) 5. Duration of hospitalization (days) 6. Any myocardial injury (troponin URL >99th percentile or a ≥ 2-fold increase if troponin is abnormal at baseline or a new >10% reduction in LVEF by echocardiography), and underlying ischemic (Fourth Universal definition) [25] or inflammatory cause 7. Venous thrombosis or thromboembolic complication confirmed by imaging 8. All stroke (NeuroARC defined) [26] 9. Acute kidney injury (AKIN criteria) [27] 10. Time (in days) to symptomatic improvement: reduction in baseline WHO ordinal score by >2 points or achievement of scores 1–3 11. Overall WHO ordinal scale for clinical improvement at 30 and 60 days Biomarkers: 1. 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). 2. Change of the SOFA from baseline. 3. 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. 4. 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 [28].

trial at 15 days 10.7% of patients were requiring their use [10]. The true 30-day event rate will be higher given that 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. Based on a recent meta-analysis the in-hospital rate of pulmonary embolism (PE) and deep venous thrombosis (DVT) in non-ICU COVID-19 patients was 10.5% and 7.4%, respectively, with about 42% of patients with PE having an identified DVT [30], resulting in a composite event rate for DVT/PE of 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. This will be balanced by the fact that imaging is not mandated in all patients in the COLSTAT trial. Finally, the incidence of acute MI and/or ischemic stroke appears to be approximately 1% based on a recent large registry [31]. The absolute sum of these event rates is approximately 52%. Therefore, using a conservative 15% overlap in events, we expect the control event rate to be 44.2% with SOC.

At the time of the initiation of this trial, evidence from small RCTs and observational studies studying statin and colchicine use in COVID-19 patients suggested that a clinically relevant 30% relative difference in the primary endpoint was a reasonable assumption for the intervention arm [20,32]. Under these assumptions, a total of 466 subjects (233 per arm) will provide ≥80% power to detect a 30% relative difference in the primary endpoint at an alpha level of 0.05 and assuming 10% of patients being lost to follow-up at 30 days. Loss to follow up will be mitigated through the use of Epic, which will allow follow-up of patients seen by any provider in the YNHH system.

Since the initiation of the COLSTAT trial, more recent trials have provided up-to-date event rates based on the new SOC. The more contemporary RECOVERY trial arm comparing colchicine to placebo in which 87% received steroids, 23% received remdesivir, and 13% received tocilizumab/sarilumab identified the following 28-day event rates based on preliminary results published on a preprint server: 25% incidence of mechanical ventilation and death in patients not requiring mechanical ventilation at time of randomization, 22% incidence of non-invasive ventilation in patients not receiving it at randomization, 4% incidence of renal replacement therapy (RRT), and 5.8% incidence of any thrombotic event (DVT/PE, MI, stroke) [33]. Under similar assumptions of event overlap the control event rate using these incidences would be 48%, thus, the initial assumed event rate remains reasonable.

Assumptions for the secondary powered endpoint were made based on internal data from COVID-19 patients admitted to the YNHH system from March through June 2020. Of the 1412 patients, >46% met the secondary powered endpoint. Using the same assumptions as above, the sample size of 466 patients would provide 85% power to detect a difference between the 2 arms.

The primary population for all analyses will be based on the intention-to-treat population defined by the assigned treatment at randomization regardless of the treatment actually received. The primary efficacy endpoint analysis will be a test of superiority of colchicine and rosuvastatin in addition to SOC compared to SOC alone with regard to progression of COVID-19 disease as assessed by the primary endpoint using the z-test with pooled variance. A subject will be defined as progressed if they experience any of the events in the primary endpoint at any time through 30 days. Secondary analyses will be performed in the as-treated population defined by the treatment actually received (defined as at least 1 dose received) and the per-protocol population defined as patients meeting eligibility criteria without major protocol deviation and receiving the assigned treatment. Prespecified subgroup analyses will include diabetes, age (<65 years versus ≥65 years), sex, race, ethnicity, hypertension, coronary artery disease, cerebrovascular disease, chronic kidney disease, heart failure, statin naïve subjects, adjunctive treatments (dexamethasone, remdesivir, tocilizumab, monoclonal antibodies, ACEi/ARBs, anticoagulation, antiplatelet agents, vaccinations, etc.), SOFA score tertiles, and WHO score on admission. Vaccinations were not widely available to the public at the time of trial initiation; however, a *post hoc* analysis by vaccination status at the time of enrollment will also be conducted. Similarly, although data on SARS-CoV-2 strain is not available, a *post hoc* subgroup analysis will also be conducted stratifying patients based on the predominant strain in Connecticut at a given time. Finally, a sensitivity analysis only including patients who had an imaging evaluation to rule out DVT/PE will be done to address concerns about ascertainment bias.

2.8. Study monitoring/committees

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. An independent data and safety monitoring board (DSMB) will be responsible for the oversight of the study, as well as the scientific merit of the trial based on evaluation of an interim analysis. There is no protocol planned pre-specified interim analyses for the purposes of altering the study design; however, interim data are provided exclusively to the data safety monitoring board.

2.9. Data extraction and validation

The primary dataset will be obtained as a direct export from Epic. For all patients, data from the index admission, including vitals, oxygen/ventilation requirements, discharge status (alive/deceased), lab values, and imaging will be exported from Epic with the assistance of the Joint Data Analytics Team (JDAT). A subset of JDAT exported data will be validated against a parallel standard Research Electronic Data Capture (REDCap) database with traditional manual data entry.

3. Current status

The trial was reviewed by FDA and exempt from IND requirement and was approved by a single IRB for the entire YNHH network of 4 hospitals. The study began enrollment in October 2020 and is currently ongoing. The protocol was amended in March 2021 to expand enrollment and add arterial/venous thromboembolic complications to the primary endpoint to increase our estimated control event rate in light of published improvement in reported outcomes in hospitalized COVID-19 patient due to improved SOC. As of August 9, 2021, 236 patients (113 active versus 124 control) have been enrolled across the 4 centers (Fig. 3).

4. Discussion

Despite improvements in SOC, mortality in hospitalized COVID-19 patients enrolled in published RCTs still remains as high as 20–30% [10–13,29,33]. Moreover, due to frequent global shortages of available treatments and the emergence of deadlier and possibly vaccine-resistant strains [34,35], the need for further treatments that are also cost effective remains. The goal of the COLSTAT trial is to address this need.

In the early stages of the pandemic, colchicine was a promising medication for the treatment of COVID-19. It is an oral anti-inflammatory agent that inhibits tubulin polymerization and microtubule formation, which inhibits any process that requires intracellular trafficking along microtubules, cell mitosis, and cell migration [36,37].

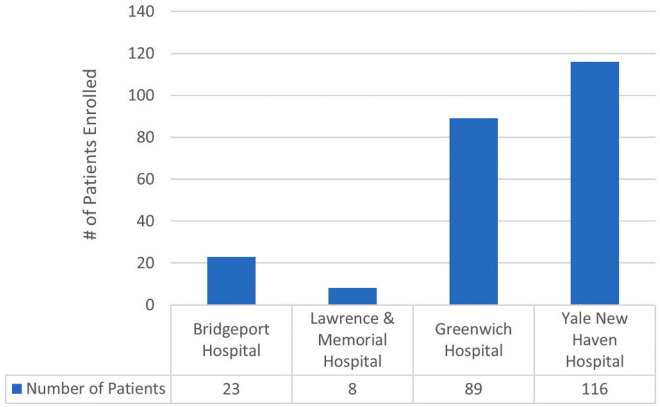

Fig. 3. Patient Enrollment by Site.

Colchicine downregulates multiple inflammatory pathways including the NLRP3 inflammasome implicated in acute lung injury [17,38] and modulates innate immunity [36,39–42]. Because of its anti-inflammatory effects, colchicine is indicated for the treatment of gout, Behcet's syndrome, familial Mediterranean fever, and pericarditis [43,44]. It has also been found to improve outcomes in patients with stable coronary artery disease or recent myocardial infarction [23,24]. With regard to COVID-19 in particular, colchicine may indirectly improve outcomes through its anti-inflammatory effects and directly by interfering with SARS-CoV-2 viral endocytosis and disrupting viral exit from the cell by preventing spike protein binding to microtubules [15,16]. Furthermore, 2 early, small, RCTs comparing colchicine to SOC in COVID-19 patients found that colchicine use reduced the risk of a 2-point deterioration on the WHO ordinal scale (1.8% versus 14.0%, $p = 0.02$) [17] and reduced duration of hospitalization (median 7.0 days versus 9.0 days, $p = 0.003$) and of supplemental oxygen requirement (median 4.0 days versus 6.5 days) [18]. The former trial also found that colchicine significantly reduced the peak concentration of D-dimer in patients (0.76 μg/mL versus 0.92 μg/mL, $p = 0.04$) [17], which is often used as a marker of coagulopathy in COVID-19 patients. The Colchicine Coronavirus SARS-CoV-2 (COLCORONA) trial (NCT04322682) investigated the effect of colchicine on non-hospitalized COVID-19 patients and found that it reduced the rate of death and hospitalization compared with placebo (4.6% versus 6.0%, $p = 0.04$) [45]. Lastly, a meta-analysis of the RCTs above and select observational studies found that colchicine improved mortality (RR 0.62, 95% CI 0.48–0.81, $p < 0.001$) [32]. It should be noted, however, that the vast majority of these studies were conducted before dexamethasone and tocilizumab were SOC. Indeed, the preliminary results of the contemporary arm of the large RECOVERY trial comparing colchicine to placebo (>10,000 patients) did not find any benefit with regard to any 28-day event including death (21% in colchicine arm versus 21% in placebo arm, $p = 0.77$), noninvasive ventilation (21% versus 23%, $p = 0.14$), mechanical ventilation (7% versus 6%, $p = 0.06$), or thrombotic events (5.7% versus 5.9%) [33]. This may be because colchicine does not provide any *additional* anti-inflammatory benefit to hospitalized COVID-19 patients given the other strong anti-inflammatory medications they now receive as SOC.

Statins have multiple pleiotropic effects beyond lipid lowering that could be beneficial during acute infections, including anti-inflammatory and antithrombotic effects, mitigation of endothelial dysfunction, and cardiac and lung protection through increased angiotensin-converting-enzyme 2 (ACE2) expression [46–49]. Because of this, multiple RCTs have studied the acute use of moderate-to-high dose statin therapy in septic and/or intubated patients with variable results [50–55]. The positive trials have demonstrated improvements in mortality or incidence of ventilator associated pneumonia [50], ICU length of stay [51], development of severe sepsis [55], and reduction in inflammatory cytokines [56]. In the case of SARS-CoV-2 in particular, statins may affect its ability to enter cells by changing the content of lipid membranes [22]. In addition, molecular docking studies have suggested that statins, including rosuvastatin, may be able to bind to and directly inhibit the main protease (Mpro) of SARS-CoV-2 with similar affinity to some known antivirals [21]. At the clinical level, multiple retrospective studies and meta-analyses have found that chronic prior statin use is associated with improved rates of mortality and/or severe disease in hospitalized COVID-19 patients [19,20]. Indeed, 1 propensity-matched analysis of 1296 hospitalized patients found that antecedent statin use was associated with markedly improved mortality (OR 0.47, 95% CI 0.36–0.62, $p < 0.001$) [19]. Again, it should be noted that the vast majority of these patients were not treated with contemporary SOC. The most recent study to address this topic is the Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomized Controlled Trial (INSPIRATION) study, which is a 2 × 2 factorial design study comparing intermediate dose versus standard dose prophylactic anticoagulation and statin therapy versus placebo in COVID-19 patients admitted to the ICU receiving

contemporary SOC. [57,58] The preliminary results of the INSPIRATION-statin study (≈300 patients per arm) were recently presented [57]. Although there was no significant improvement in the statin arm with regard to the 30-day primary composite endpoint of venous or arterial thrombosis, ECMO, or all-cause mortality (OR 0.84, 95% CI 0.58–1.21, $p = 0.35$) there was a numerical benefit for each individual endpoint. Additionally, in the subgroup of patients who had symptoms for ≤7 days, there did appear to be benefit with regard to the primary endpoint (OR 0.60, 95% CI 0.37–0.99, $p = 0.055$). This is particularly promising because the COLSTAT trial aims to enroll non-ICU patients who are presumably earlier in their disease course and thus have greater potential for benefit. Moreover, while the INSPIRATION-statin trial used a medium-intensity statin dose (atorvastatin 20 mg), the COLSTAT trial uses a high-intensity statin (rosuvastatin 40 mg) that is about 4 times more potent than the dose in the INSPIRATION trial. Notably the effect size seen in this trial for the patients with ≤7 days of symptoms was 23%, making a 30% assumed effect size for the COLSTAT trial reasonable.

The COVID-19 pandemic has emphasized the need for streamlining research infrastructure in order to answer important questions more quickly and efficiently. One such method is leveraging the power of EHR, which can be used for faster screening and enrollment, randomization, intervention delivery, and easy remote follow-up for endpoint ascertainment and monitoring. EHR is increasingly being used in clinical trials to some degree [59,60]. The vast majority of clinical trials to date that utilize EHR specifically test EHR-based interventions such as alerts or clinical decision support tools [59,61], although trials testing non–EHR-based interventions such as medical treatments have begun to utilize EHR as well at various stages [62,63]. The pragmatic COLSTAT trial is among the first trials to fully use EHR in all phases of the trial and demonstrates its utility moving forward for trials in other domains as well.

5. Limitations

This is an open-label pragmatic trial based on standard of care, which comes with inherent limitations of ascertainment, measurement, and observer expectancy bias. Furthermore, the rapidly evolving nature of the pandemic, with new treatments, vaccinations, and virus variants will likely result in a heterogenous population enrolled in the trial. The sensitivity analyses in the various subgroups detailed above will be used to identify if any of these factors significantly affected the results.

6. Conclusions

The goal of the COLSTAT trial is to identify if 2 commonly available, well studied medications can reduce the severity of COVID-19 in hospitalized patients. Despite inherent limitations of rapidly evolving treatments, disease variants and severity of disease, COLSTAT is designed to be a pragmatic trial and will demonstrate the power of using the EHR to improve efficiencies and enrollment in clinical trials in an adapting landscape.

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Declaration of Competing Interest

None.

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