Early Institution of Tocilizumab Titration in Non-Critical Hospitalized COVID-19 Pneumonitis (COVIDOSE)

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Ad hoc consultative expertise

Protocol Type / Version # 1.6/ Version Date: 04/20/2020

Study Design: An operating committee-guided multi-arm, multi-step dose escalation/de-escalation trial.

Eligible Patients: Hospitalized, non-critically ill patients with a diagnosis of COVID-19 pneumonitis

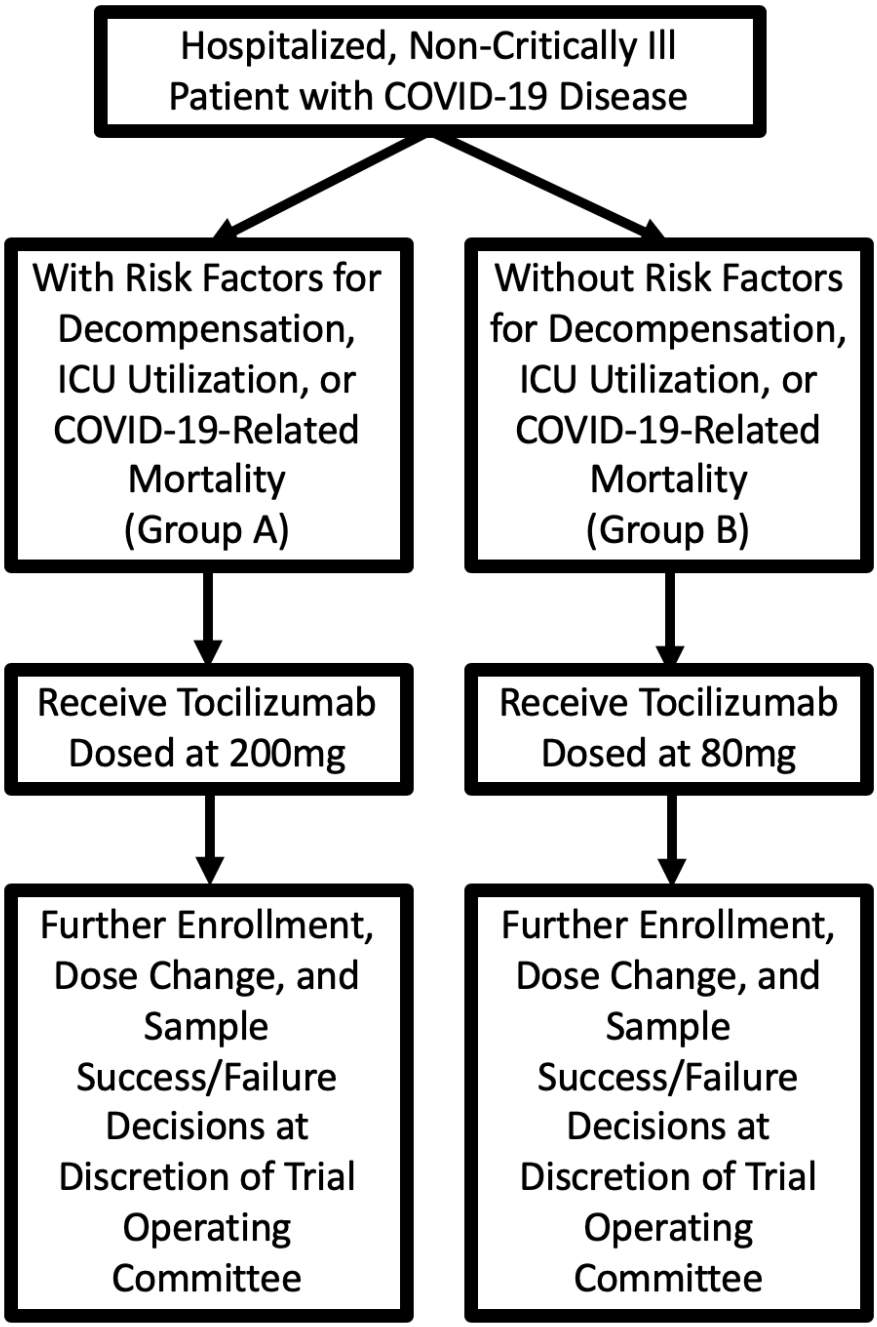
Primary Objectives:
1. To establish proof of concept that tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients with clinical risk factors for clinical decompensation, intensive care utilization, and death.

2. To establish proof of concept that low-dose tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients without clinical risk factors for clinical decompensation, intensive care utilization, and death.

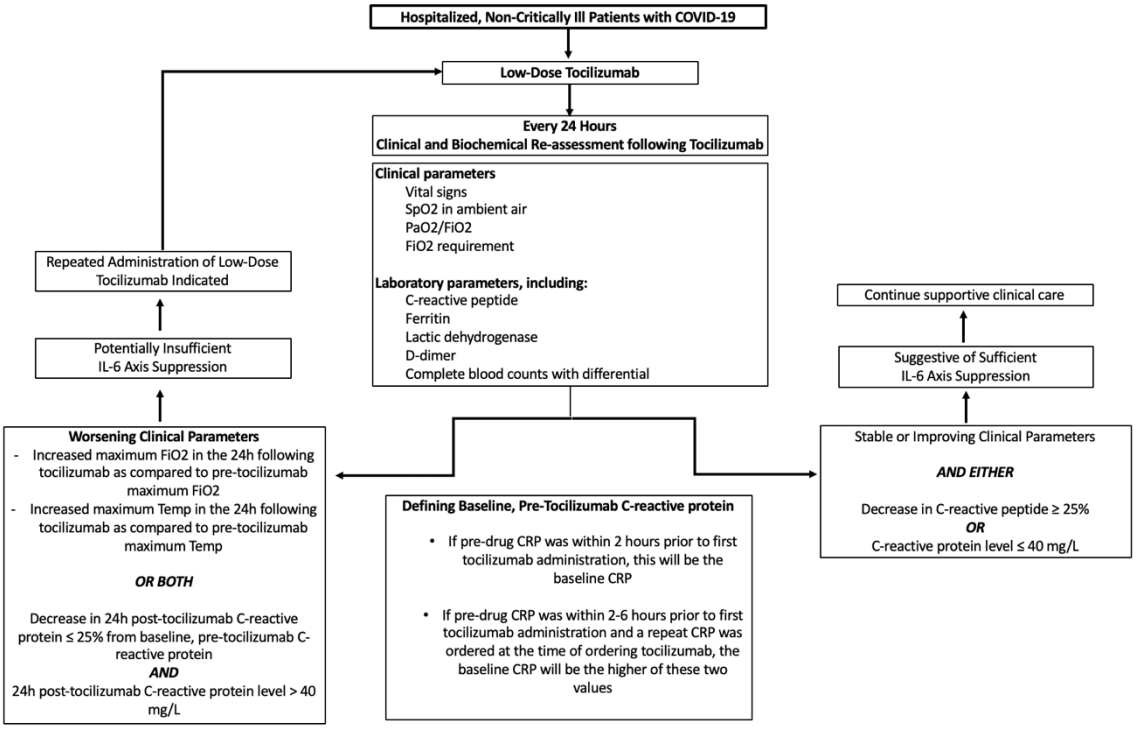
3. To estimate the minimum effective dose of tocilizumab, as assessed by early clinical and biochemical markers of resolution of hyperinflammation, in hospitalized, non-critically ill patients with moderate COVID-19 pneumonitis, with and without clinical risk factors for clinical decompensation, intensive care utilization, and death.

Secondary Objectives:
To evaluate 28-day overall survival, survival to hospital discharge, rate of progression of COVID-19 pneumonitis, rate of non-elective mechanical ventilation, number of days to mechanical ventilation (invasive and non-invasive), number of days requiring mechanical ventilation, rate of vasopressor support utilization, number of days to vasopressor support, and number of days of vasopressor support in non-critically ill patients with COVID-19 pneumonitis who are treated with tocilizumab.

OVERALL STUDY SCHEMA:



PROPOSED TREATMENT AND RE-DOSING STRATEGY FOR LOW-DOSE TOCILIZUMAB:



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1 INTRODUCTION

1.1 Background and Rationale

1.1.1 COVID-19 and Global Pandemic

The global pandemic of coronavirus disease-2019 (COVID-19), secondary to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), represents an emergent threat to public health, with a quoted mortality rate among inpatients greater than 25% (1). Containment strategies have been employed to varying degrees and effects in Western nations, now necessitating mitigation strategies in overwhelmed hospitals to effectively address COVID-19. Limited intensive care unit- (ICU) level resources such as mechanical ventilation and other in-hospital resources such as bedding space have played a significant role in the poor clinical outcomes associated with COVID-19 (2-4). Moreover, the throughput and length of hospitalization of patients requiring acute care beds may play a role in the "logjam" of available resources in a pandemic. Therefore, early identification of patients at risk for clinical decompensation, imminently preventing their decompensation so as to preserve as many ICU-level resources as possible, and decreasing the length of stay of non-critically ill patients are all crucial at a public health level to navigate the COVID-19 pandemic.

1.1.2 COVID-19 Disease Risk-Stratification

Varying clinical presentations of COVID-19 disease exist. The pneumonitis associated COVID-19 disease exists on a continuum, ranging from (on one extreme) bilateral infiltrates and associated respiratory failure, hyperinflammation, and septic shock leading to death to (at the other extreme) absence of pulmonary infiltrates and very mild symptoms. For the purposes of this study, patients meet diagnostic criteria for COVID-19 pneumonitis when they have: 1) positive SARS-CoV-2 viral polymerase chain reaction test and 2) evidence of an infiltrate on chest imaging. Patients with COVID-19 disease may be admitted to the hospital for varying reasons. It is possible that patients with COVID-19 disease may be admitted to the hospital and *not* have COVID-19 pneumonitis. Those patients with COVID-19 disease who do not have pulmonary infiltrates are generally at low risk for progression to pneumonitis and clinical decompensation, ICU resource utilization, and death. For the purposes of our study, we will focus primarily on hospitalized patients with signs of COVID19 pneumonitis who are not designated to be critically ill as delineated by aforementioned parameters (Figure 1). Based on previously published data, (1) we can broadly risk-stratify patients who meet diagnostic criteria for pneumonitis according to their risk of clinical decompensation, intensive care unit (ICU) utilization, and death. The first division in the risk stratification schema is between patients who are critically ill (Figure 1) and those

who are not. Within the subpopulation who are not critically ill, there are those with relatively high risk for decompensation, ICU utilization, and COVID-19-related mortality (Group A; Figure 2) and those with relatively low risk for these same outcomes (Group B; Figure 3).

1.1.2.1 Defining the Subpopulation of Critically Ill Patients with COVID-19 Pneumonitis

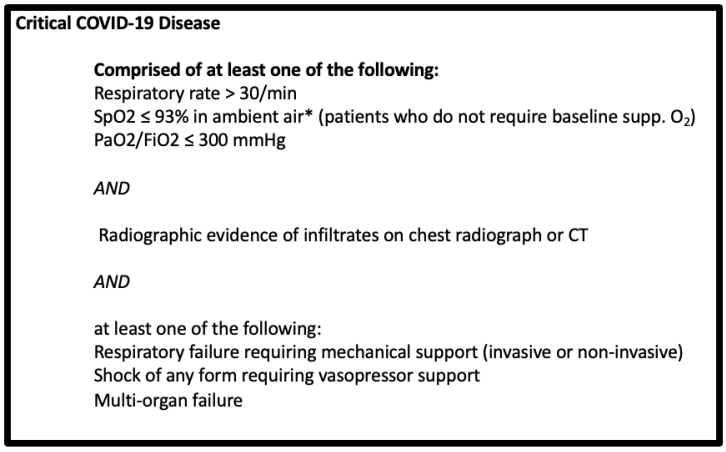

Figure 1. Clinical and radiographic characteristics of patients with Critical COVID-19 disease.

First are critically ill patients with COVID-19 pneumonitis who are already utilizing near-ICU or ICU-level resources. These patients (Figure 1) have polymerase chain reaction (PCR)-proven SARS-CoV-2 infection, radiographic evidence of infiltrates, and physiologic signs of pneumonitis and COVID-19 related hyperinflammation marked by one or more of either respiratory rate greater than or equaled to 30 per minute, oxygen saturation of 93% or less in ambient air (for patients without baseline supplemental oxygen requirement), or a partial pressure of oxygen (PaO2)-fraction of inspired oxygen (FiO2) ratio of less than or equal to 300 mmHg. In addition, critical patients will be defined as having one or more of either respiratory failure requiring mechanical ventilation (invasive or non-invasive), shock of any form requiring the use of a vasopressor medication, or multi-organ failure.

1.1.2.2 Defining and Risk-Stratifying within the Subpopulation of Non-Critically Ill Patients with COVID-19 Pneumonitis

The remaining patients with COVID-19 pneumonitis who are admitted to the hospital are those non-critically ill patients who do not meet criteria for critical COVID-19 disease. These patients have risk, however, of clinical decompensation, utilization of ICU-level resources, and ultimately COVID-19 disease-related mortality. This population of patients can itself be thought of as two subpopulations: One has relatively high risk for progression to critical COVID-19 disease and ultimately COVID-19 disease-related

mortality (Figure 2) (hereafter 'Group A'). Risk factors, as determined by a consensus of a multi-disciplinary panel of experts, include epidemiologic risk factors related to medical history and laboratory-based signs of hyperinflammation. The second subpopulation is comprised of patients (hereafter 'Group B') (Figure 3) who have COVID-19 disease but lack the epidemiologic or laboratory-based risk factors known to marginally increase the probability of progression to critical COVID-19 disease or COVID-19-related mortality. Both groups have risk of clinical decompensation, utilization of ICU-level resources, and COVID-19 disease-related mortality and may benefit from early treatment with medications aimed at managing COVID-19 disease-related CRS. As a public health measure, early treatment may help to preserve limited ICU resources.

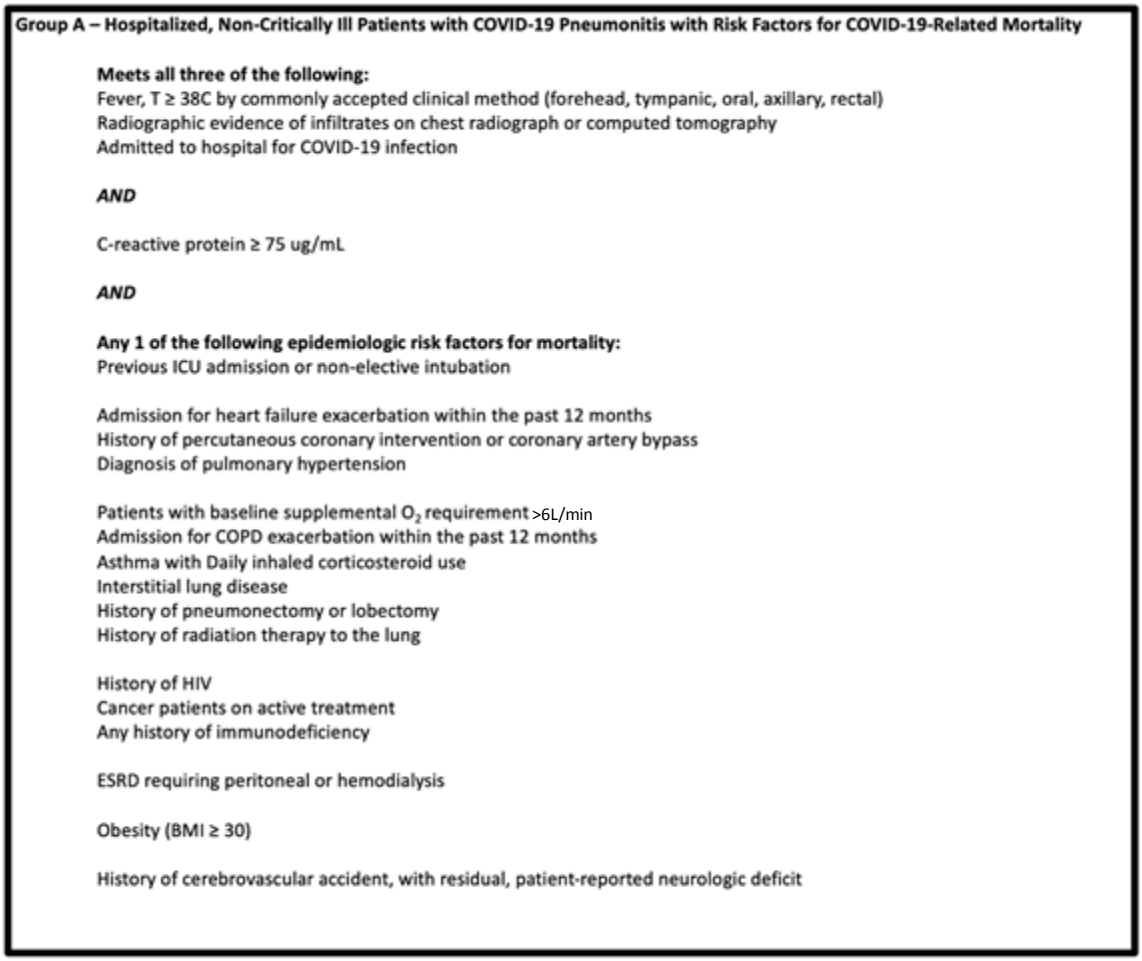

Figure 2. Group A. Clinical, laboratory, and epidemiologic characteristics of hospitalized, non-critically ill patients with COVID-19 pneumonitis at higher risk for clinical decompensation, ICU utilization, and COVID-19 disease-related mortality.

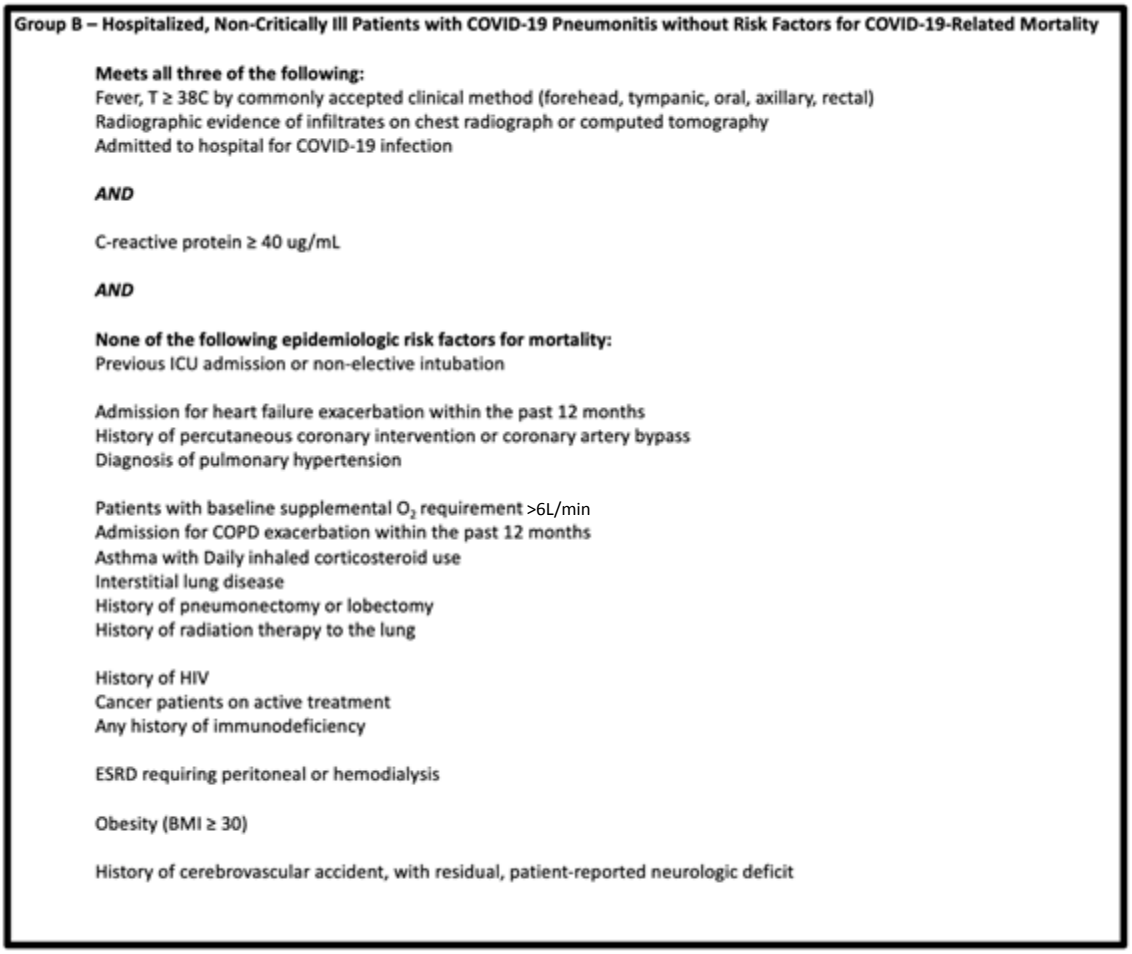

Figure 3. Group B. Clinical and laboratory characteristics of hospitalized, non-critically ill patients with COVID-19 pneumonitis at relatively lower risk for clinical decompensation, ICU utilization, and COVID-19 disease-related mortality.

1.1.3 Parallels Between COVID-19 and Chimeric Antigen Receptor T-Cell (CAR-T)- Related Cytokine Release Syndrome (CRS)

COVID-19's high mortality may in part be driven by hyperinflammation resembling the cytokine storm often identified in hemophagocytic lymphohistiocytosis and cytokine release syndrome (CRS), offering the hope that immunosuppressive therapies commonly used to treat CRS – such as the interleukin-6 (IL-6) receptor-targeted monoclonal antibodies tocilizumab or sarilumab and IL-6 targeted monoclonal antibody siltuximab – can be used to reduce mortality in COVID-19 (Figure 4) (5). Emerging evidence shows marked elevation of serum IL-6, C-reactive protein (CRP), lactic dehydrogenase, and ferritin in patients with COVID-19, with the degree of elevation correlating with severity of disease (1, 6, 7). Early data suggest IL-6 axis suppression has promise. Retrospective analysis of severe to critical COVID-19 patients receiving tocilizumab 400 mg (approximately 6.67 mg/kg using average Chinese body weight) demonstrated that greater than 75% of patients had rapid resolution (i.e., within 24-72 hours following administration) of both clinical and biochemical signs (fever and CRP, respectively) of

hyperinflammation with only a single tocilizumab dose (6). To date, no prospective investigation on the topic – tocilizumab for the treatment of COVID-19 associated CRS – has been published.

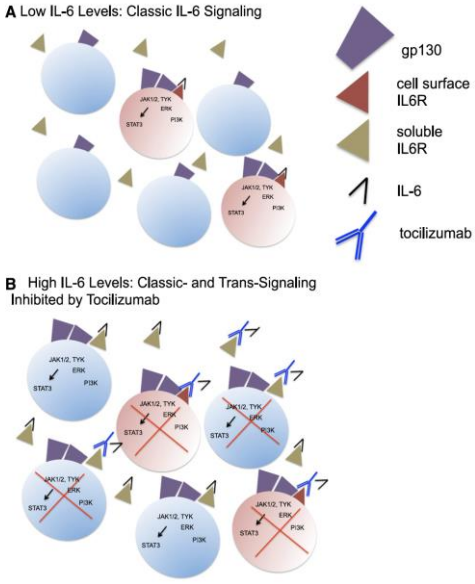

Figure 4. Interleukin-6 signaling in cytokine release syndrome (CRS) in chimeric antigen receptor T-cell (CAR-T). In normal circumstances (panel A), classic IL-6 signaling, marked by IL-6 binding only to cell-bound IL-6 receptors (IL-6R), predominates. IL-6-axis signaling typically only occurs in neutrophils, macrophages, hepatocytes, and select T-cells. Under circumstances such as CAR-T-mediated CRS (B) and possibly COVID19-mediated CRS, IL-6 levels are markedly elevated, leading to pro-inflammatory *trans* IL-6-axis signaling and resultant systemic inflammation akin to sepsis. (Image first published in Lee *et al*, Blood, 2014. Legend is independently written.)

1.1.4 Justification for C-Reactive Protein Cutoffs

Evidence collected thus far in COVID-19 suggests C-reactive protein (CRP) as a useful proxy marker for serum IL-6 levels as well as COVID-19 disease-related inflammation in hospitalized patients, both critically ill and non-critically ill (8-10). Early reports from the University of Chicago experience demonstrate that admission CRP is elevated in approximately 90% of hospitalized patients with COVID-19 disease (using an institutional normal range of < 5 ug/mL). Critically ill patients with COVID-19 disease tend to have higher CRP than non-critically ill patients (mean, 91 vs 66 ug/mL) (Natasha Pettit, COVID-19 Response Team, personal communication). The goal of the overarching treatment strategy discussed in 1.2.2 is to provision potentially efficacious therapy to the greatest number of patients likely to benefit from tocilizumab while still preserving an adequate supply for critically ill patients. Approximately 50% of hospitalized, non-critically ill patients with COVID-19 have CRP of < 40 ug/mL. (Natasha Pettit, COVID-19 Response Team, personal communication). An additional 30% of patients have CRP between 41 and 75 ug/mL, with the final 20% of hospitalized, non-critically ill COVID-19 patients having CRP greater than 75 ug/mL (Natasha Pettit, COVID-19 Response Team, personal communication).

1.1.5 Anticipated Drug Shortages in the Treatment of COVID-19

Even if immunosuppressive monoclonal antibodies are efficacious therapies, challenges remain. As in the case of hydroxychloroquine, aggregate demand for anti-IL6 therapies driven by off-label utilization could quickly outstrip available supplies(11, 12).

Moreover, the supply of these anti-IL6 therapies may not be efficiently matched to hospitals expected to bear the brunt of COVID-19 (13). To overcome the drug supply/demand mismatch, three challenges must be overcome: 1) demand must be reduced through maximal containment measures, 2) the available medication's distribution channels must be improved, and 3) the *effective* supply of the medications must be increased by ramping up manufacturing and extend anti-IL-6 therapy as much as possible.

1.1.6 **Interventional pharmacoeconomics to increase effective supply**

We can draw on lessons from the new field of interventional pharmacoeconomics (IVPE) to increase the effective supply of anti-IL-6 therapy (14). Many monoclonal antibodies used in both oncologic and rheumatologic indications in the *outpatient* setting have labeled doses and schedules aimed at maintaining a therapeutic concentration for weeks. In contrast, in the inpatient setting, where a patient's primary problem is expected to be temporary and on the order of days, a lower and more frequent dosing of a monoclonal antibody is preferable. This approach helps to minimize the total amount of medication used and reduce the frequency and/or duration of adverse events. This pharmacological line of reasoning is germane to COVID-19 and is a plausible strategy to conserve use of potentially efficacious and supply-limited anti-IL6 therapies. Moreover, there is medical rationale in COVID-19: Immunosuppression for long periods of time of patients who are expected to have long inpatient hospital stays may increase their risks of nosocomial infection or bacterial superinfection, both of which have been concerns in patients with coronavirus infections (15, 16).

1.2 **Tocilizumab**

1.2.1 **Clinical Studies**

Tocilizumab was originally developed for outpatient, every four-weeks administration in rheumatoid arthritis (RA), giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis at a labeled dose of 8 mg/kg, with approval based on improvement in the American College of Rheumatology (ACR) 20 score (17). Dose-finding studies revealed a dose-related reduction in Disease Activity Score in 28 joints (DAS28) beyond 4 weeks at doses 4mg/kg and 8mg/kg (17). In its subsequent new drug application for treating CRS in chimeric antigen receptor T cell (CAR T) therapy, no formal dose-finding study was performed and tocilizumab was approved after the 8mg/kg dose, provisioned up to four times at least eight hours apart, led to resolution of CRS within a 14-day period of time (the primary outcome measure for these purposes) (17). Response data from Food and Drug Administration (FDA) filings, however, suggest a 4 mg/kg dose had similar efficacy (table 18, reference 5) (18). Critically, lower doses were not studied (18). No common CRS biomarkers such as ferritin or C-reactive peptide (CRP) response were included as part of tocilizumab's FDA filings (18). The FDA's own review stated: "It was notable that some patients in the Treated Population had resolution of CRS by day 14 after receiving tocilizumab 4 mg/kg, suggesting that a dose lower than recommended might be effective" (18).

1.2.2 A Treatment Strategy Incorporating Low-Dose Tocilizumab

At an individual patient level, utilizing the minimally effective dose of a drug (tocilizumab) can optimize efficacy with minimalization of adverse events. On a more global scale, the logic behind a grand strategy for COVID-19 pandemic mitigation efforts is to proactively utilize one rare resource (tocilizumab) to prevent utilization of another, more limited resource (ICU-level care), rather than waiting until a patient is already committed to the most limited resource (ICU-level care) to then expend another limited resource (tocilizumab). The goal of the overarching treatment strategy is to provision potentially efficacious therapy to the greatest number of patients likely to benefit from tocilizumab while still preserving an adequate supply for critically ill patients (Figure 5) (12).

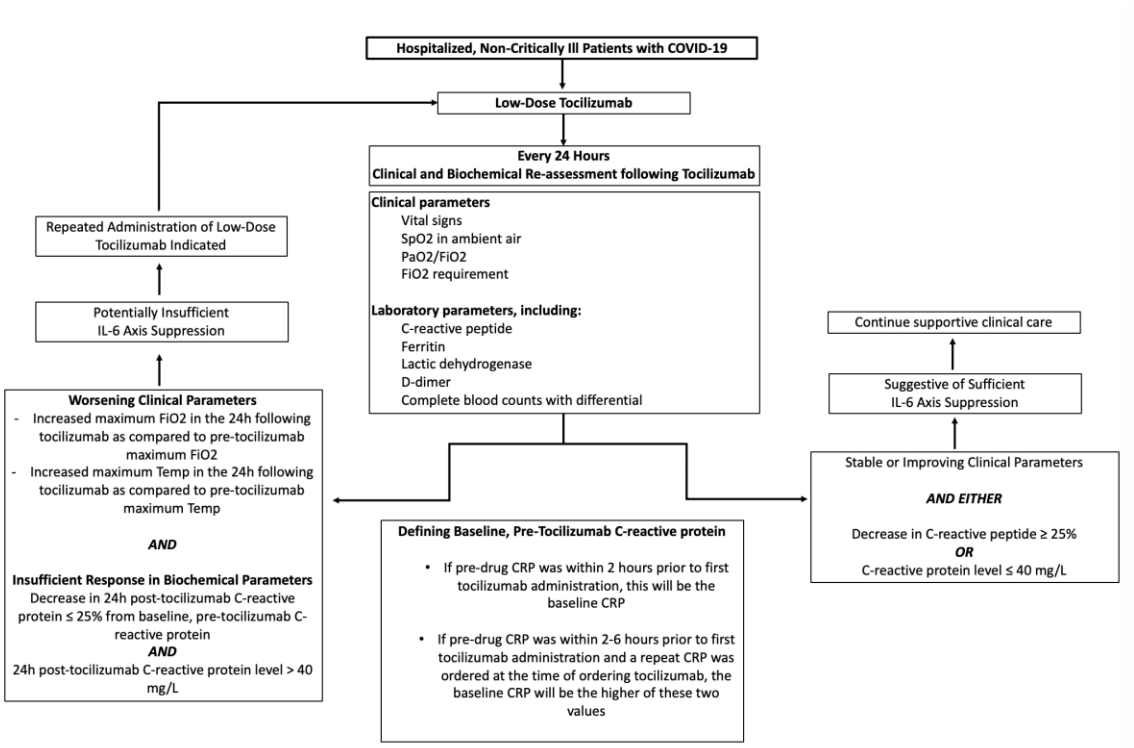

Figure 5. Utilization of low-dose tocilizumab in hospitalized, non-critically ill patients with COVID-19 disease to prevent clinical decompensation, ICU utilization, and COVID-19-related death.

Tocilizumab's effectiveness in CRS after CAR-T therapy has led to off-label treatment of CRS from COVID-19 infections with preliminary evidence showing efficacy (6). Unfortunately, as previously stated, tocilizumab is in limited supply. In this context, we have proposed the development of alternative treatment regimens for supportive care of COVID-19 (Figure 5) with the aim of providing therapy for the greatest number of patients likely to benefit. Hospitalized, non-critically ill patients with COVID-19 with and without risk factors for developing severe disease may be prime candidates for treatment with tocilizumab. Given the much lower IL-6 concentrations in COVID-19 compared to CRS, we envision that single doses less than 400 mg will be effective (7, 19). To date, tocilizumab 400 mg is the adopted standard of care dose, representing a

dose of approximately 5 mg/kg (based on average body weight in the United States). The speed with which both clinical and biochemical improvements in COVID-19-related hyperinflammation are seen in patients with COVID-19 treated with tocilizumab suggests rapid readout within 24 hours is possible (Figure 5) (6). Patients will be reassessed at 24 hour intervals. Factors assessed will include: overall clinical status (specific focus on maximum supplemental oxygen required over the preceding 24 hours, fever curve and maximum temperature over the preceding 24 hours) as well as biochemical parameters that parallel IL-6 axis-suppression (with focus on C-reactive peptide (CRP) measured at approximate 24 hours after the initial dose and then daily thereafter) (6). Similar approaches may be useful in safely reducing the labeled doses of other IL-6 axis-suppressing therapies and IL-1 antagonists (e.g., anakinra) to more COVID-19-appropriate doses, thereby increasing effective supply.

Patients will be considered for a total of 2 doses of tocilizumab. Participants will be followed up evaluation of re-dosing 24-48 hours after first tocilizumab dose. Patients will be considered for re-dosing of tocilizumab if they meet one or more of the clinical criteria *and* the biochemical criteria below:

- Clinical criteria
    - Increased maximum supplemental oxygen required over approximately 24 hours following the first tocilizumab dose compared to pre-dosing or baseline supplemental oxygen requirements *and* determined to be associated with COVID19 pneumonitis as determined by primary team *or*
    - Increased maximum temperature over approximately 24 hours following the first tocilizumab dose compared to maximum temperature in the 24 hours prior to first tocilizumab administration

AND

- Biochemical criteria
    - CRP decrease of <25% of baseline CRP and >40mg/L:
        - This follow-up CRP will be measured >=24 hours post first tocilizumab dose and >=24 hours since the draw of the CRP within 2 hours of first dose administration.
        - Baseline CRP
            - If pre-drug CRP was within 2 hours prior to first tocilizumab administration, this will be the baseline CRP
            - If pre-drug CRP was within 2-6 hours prior to first tocilizumab administration and a repeat CRP was ordered at the time of ordering tocilizumab, the baseline CRP will be the higher of these two values

Re-dose if meets both clinical *and* biochemical parameters met:	
1. Patient would meet **clinical** parameter if	Follow-up-Tmax* > Pre-TCZ Tmax *or* Follow-up-O2-required* > Pre-TCZ O2 required
2. Patient would meet **biochemical** parameter if	Follow-up- CRP[†]>40mg/L *and* Follow-up CRP[†] decrease is <25% of Baseline CRP[#]

*Max in 24hours *post*TCZ compared to Max value in 24hours *pre*TCZ and associated with COVID19 per primary team
[†]Follow up CRP will be >= 24 hours after first tocilizumab dose *and* >=24 hours after baseline CRP
[#]Baseline CRP will be defined according to when results in reference to drug administration as follows:

- If pre-drug CRP was within 2 hours prior to first tocilizumab administration, this will be the baseline CRP
- If pre-drug CRP was within 2-6 hours prior to first tocilizumab administration and a repeat CRP was ordered at the time of ordering tocilizumab, the baseline CRP will be the higher of these two values

1.2.3 Dose-finding Studies for Tocilizumab in COVID-19

No dose-finding studies have been completed for tocilizumab in COVID-19 disease or CAR-T-related CRS.

1.2.4 Justification for Proposed Tocilizumab Dosing

Group A
Hospitalized, non-critically ill patients with COVID-19 disease who have known epidemiologic risk factors and/or evidence of incipient hyperinflammation represent a group with significantly higher than baseline risk for clinical decompensation, utilization of ICU-level resources, and COVID-19 disease-related mortality. The risk of inhibiting innate antiviral response with high- or standard of care dose tocilizumab is not insignificant. We therefore believe it prudent to begin proactive treatment of these patients with a tocilizumab dose that is lower than reported by others. The current adopted standard of care dose in the critical setting is 400mg (20, 21). We propose a starting dose of 200mg.

Group B
Hospitalized, non-critically ill patients with COVID-19 disease who do not have known epidemiologic risk factors and evidence of incipient hyperinflammation represent a group of patients with risk for clinical decompensation, utilization of ICU-level resources, and COVID-19 disease-related mortality that is higher than that of the global population (which includes all patients with COVID-19, both inpatient and outpatient) but lower than the mean risk of the inpatient population (critically-ill COVID-19 patients and Group A patients). This is a non-trivial, albeit relatively smaller risk of clinical decompensation, utilization of ICU-level resources, and COVID-19 disease-related mortality. We believe it merits provision of a dose of tocilizumab approximately proportional to this population's risk.

Clinical guidance comes from the rheumatoid arthritis literature in the perioperative period in order to understand a) the impact and b) the dose of tocilizumab to reduce fever

and inflammatory markers in patients undergoing a major physiologic stressor. In a case-control study of patients with rheumatoid arthritis, investigators identified 22 patients with rheumatoid arthritis who received tocilizumab 8mg/kg as outpatients in the run-up to surgery (22). Mean time of tocilizumab provisioning prior to surgery was 16 days. Tocilizumab-treated patients had increases in body temperature on post-operative days 1 and 2 that were approximately one-half of rheumatoid arthritis control patients not treated with tocilizumab (22). Tocilizumab-treated patients also achieved suppression of the post-operative doubling in CRP identified in patients with rheumatoid arthritis who did not receive tocilizumab (22). Based on prior pharmacokinetic work and Food and Drug Administration review, the tocilizumab drug concentration at this time (16 days following administration) in patients treated with tocilizumab is predicted to be approximately 30 ug/mL (23). We infer that this concentration of tocilizumab is sufficient to blunt temperature and CRP increases in times of physiologic stress. The pharmacologically implied one-time dose of tocilizumab needed to achieve a Cmax of 30 ug/mL is between 50 and 100mg. Given this line of pharmacologic reasoning and tocilizumab's vial sizes of 80mg, 200mg, and 400mg, we therefore propose beginning with a dose of 80mg in Group B patients.

1.2.5 **Justification for Proposed Changes to Tocilizumab Dosing**

Prior investigations show there is no material difference in the rates of resolution of CRS at 14 days, the clinically relevant endpoint, between tocilizumab 4 mg/kg and 8 mg/kg, opening the possibility that a significantly lower dose could be used, especially given the lower levels of IL6 in COVID-19 infection CRS than in CAR-T-related CRS (18). Additionally, CRS symptoms from CAR-T usually resolved with only 1 or 2 doses of tocilizumab (18). Warning signs, then, of inefficacy likely will not become apparent until a truly ineffective dose of tocilizumab is reached. De-escalation of the tocilizumab dose therefore will be guided by rapidly ascertainable clinical and biochemical endpoints (1.3.1) and cautious de-escalation is warranted. To that end, de-escalations from cohort to cohort will be determined by the study's Operating Committee (discussed in section 5.3) and will not exceed 50%. Therefore, if evidence of efficacy of tocilizumab 200mg in the first Group A study cohort, the dose may be reduced to a *minimum* of 100mg in the second Group A study cohort. If evidence of efficacy of tocilizumab 100mg in the second Group A study cohort, the dose may be reduced to a *minimum* of 50mg in the third Group A study cohort, and so on. The same logic will apply to Group B study cohorts, with a starting dose of 80mg (1.2.3). Given the risks associated with excessive immunosuppression in patients with known viral infection, dose increases will be approached similarly but with a *maximum* cohort-to-cohort increase of 100%: For example, if evidence of inefficacy of tocilizumab 200mg in the first Group A study cohort, the dose may be increased to a *maximum* of 400mg in the second Group A study cohort. Dosing changes will be at the discretion of the trial's Operating Committee (discussed in section 5.3).

1.3 Endpoints

1.3.1 The Need for Rapid Endpoints

COVID-19 disease is a rapidly changing landscape with acute pressures on the US healthcare system and individual patients. Anecdotes – but not yet evidence – abound of patients rapidly decompensating after many hours, and sometimes days, of clinical stability. In a rapidly evolving situation, the presence of new clinical data points including changes in vital signs and laboratory parameters are necessary to guide clinical decisions. By the same token, evaluation of the efficacy of provisioned medications is necessary so as to guide clinical and study management. In line with the treatment strategy described in 1.2.2 and the behavior of critically ill patients with COVID-19 who were treated with tocilizumab (6), as well as given the circumstances of expected drug shortages and a need to make rapid decisions about redosing and dose changes, we propose incorporation of 24-hour clinical and biochemical endpoints. Mechanism-specific endpoints such as cytokine panels or direct measurement of IL-6 levels are send-out labs at the University of Chicago Medicine and therefore cannot be relied upon in the clinical context to make judgments about the efficacy of a given dose of tocilizumab.

1.3.2 CRP is correlated with IL-6-axis signaling

Prior literature on serologic markers of inflammation in COVID-19 disease show markedly elevated levels of both CRP and IL-6.(7) Cytokines are not frequently obtained at the University of Chicago Medicine. Because of turnaround time of > 48 hours (itself driven by pre-analytic variable of having to be sent to a reference laboratory), IL-6 cannot be directly measured and used as a dynamic measure of tocilizumab activity in clinical practice at the University of Chicago Medicine.

Prior work from the immunology literature demonstrates a strong connection between CRP elevation and the presence of IL-6 signaling (24), with IL-6-axis signaling serving as the predominant inducer of CRP expression (25). In the rheumatoid arthritis disease state in which the IL-6 axis is not targeted with therapy, CRP and IL-6 are tightly correlated, as well. Though tocilizumab administration is typically followed by a *rise* in serum IL-6 levels (23), CRP declines, suggesting a decrease in IL-6 axis signaling. Within the context of COVID-19, IL-6 and CRP are correlated, as well (8).

1.3.3 CRP and Fever Briskly Respond to Tocilizumab in COVID-19

Emerging evidence from the COVID-19 disease literature suggests critically ill patients treated with tocilizumab 400mg experience rapid improvement in fever and CRP levels(6, 26). Based upon our independent evaluation of the data available from the Xu, *et al* preprint and an estimated CRP half-life of 19 hours,(27) we infer that approximately 85% of critically ill patients with COVID-19 treated with tocilizumab 400mg would experience either a CRP decline of > 25% or a normalization of CRP to < 10 ug/mL within 24 hours of dose administration ((6), reconstituted data are available upon request). Furthermore, *all* febrile patients with COVID-19 disease who were treated

with tocilizumab 400mg experienced resolution of their fever within 24 hours of dose administration ((6), reconstituted data are available upon request) On the basis of these data and the absence of a dose-response relationship for tocilizumab in CAR-T-related CRS (1.2.4), *any* effective dose of tocilizumab should have clinical and biochemical effects similar to those of the 400mg dose.

2 OBJECTIVES

2.1 Hypotheses

1. Tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients with clinical risk factors for clinical decompensation, intensive care utilization, and death.

2. Low-dose tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients with and without clinical risk factors for clinical decompensation, intensive care utilization, and death.

3. There is a minimum effective dose of tocilizumab, lower than that of the Food and Drug Administration-labeled dose for the mitigation of CAR-T-related CRS, for the prevention of COVID-19 pneumonitis-related CRS in hospitalized, non-critically ill patients admitted for COVID-19 pneumonitis.

2.2 Primary Objectives

1. To establish proof of concept that tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients with clinical risk factors for clinical decompensation, intensive care utilization, and death, as determined by the clinical outcome of resolution of fever and the biochemical outcome measures of time to CRP normalization for the individual patient and the rate of patients whose CRP normalize.

2. To establish proof of concept that low-dose tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients without clinical risk factors for clinical decompensation, intensive care utilization, and death, as determined by the clinical outcome of resolution of fever and the biochemical outcome measures of time to CRP normalization for the individual patient and the rate of patients whose CRP normalize.

3. To estimate the minimum effective dose of tocilizumab, as assessed by early clinical and biochemical markers of resolution of hyperinflammation, in hospitalized, non-critically ill patients with COVID-19 pneumonitis, with and without clinical risk factors for clinical decompensation, intensive care utilization,

and death, as determined by the clinical outcome of resolution of fever and the biochemical outcome measures of time to CRP normalization for the individual patient and the rate of patients whose CRP normalize.

a. Failure rates, determined at 24-hour intervals following tocilizumab administration
b. Biochemical and clinical response rates, determined at 24-hour intervals following tocilizumab administration
c. Time to discharge
d. Utilization of and length of utilization of ICU-level resources (mechanical ventilation, vasopressors)
e. Overall survival at 28 days following administration of tocilizumab

3 PATIENT SELECTION

3.1 Number of Subjects

We anticipate enrollment of 5 patients in Group A and 5 patients in Group B in the first two weeks of the study's opening. Further enrollment will be determined by the trial's Operating Committee. The trial's Operating Committee will meet within the first two weeks of the start of study (and likely sooner) and at least every two weeks thereafter (and likely more frequently). Further enrollment, dose changes, and changes to stratification criteria or redosing parameters (based on iterative assessments, as detailed in 5.3) will be determined by the Operating Committee by unanimous consent of the four voting members.

3.2 Inclusion Criteria

- Adults ≥ 18 years of age
- Approval from the patient's primary service
- Admitted as an inpatient to University of Chicago Medicine
- Fever, documented in electronic medical record and defined as: T ≥ 38*C by any conventional clinical method (forehead, tympanic, oral, axillary, rectal)
- Positive test for active SARS-CoV-2 infection
- Radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT)
- Ability to provide written informed consent on the part of the subject or, in the absence of decisional capacity of the subject, an appropriate surrogate (e.g. a legally authorized representative).

3.3 Exclusion Criteria

- Concurrent use of invasive mechanical ventilation (patients receiving non-invasive mechanical ventilation [CPAP, BiPap, HHFNC] are eligible)
- Concurrent use of vasopressor or inotropic medications

- Previous receipt of tocilizumab or another anti-IL6R or IL-6 inhibitor.
- Known history of hypersensitivity to tocilizumab.
- Patients who are actively being considered for a study of an antiviral agent that would potentially exclude concurrent enrollment on this study.
- Patients actively receiving an investigational antiviral agent in the context of a clinical research study.
- Diagnosis of end-stage liver disease or listed for liver transplant.
- Elevation of AST or ALT in excess of 10 times the upper limit of normal.
- Neutropenia (Absolute neutrophil count < 500/uL).
- Thrombocytopenia (Platelets < 50,000/uL).
- On active therapy with a JAK2-targeted agent, which include the following:
    - Tofacitinib
    - Baricitinib
    - Upadacitinib
    - Ruxolitinib

- On active therapy with a biologic immunosuppressive agent, which include the following biologics and any biosimilar versions thereof:
    - Alemtuzumab
    - Blinatumomab
    - Brentuximab
    - Daratumumab
    - Elotuzumab
    - Ibritumomab
    - Obinutuzumab
    - Ofatumumab
    - Ocrelizumab
    - Rituximab
    - Inotuzumab
    - Gemtuzumab
    - Tositumumab
    - Moxetumomab
    - Polatuzumab
    - Abatacept
    - Adalimumab
    - Belimumab
    - Certolizumab
    - Eculizumab
    - Etanercept
    - Golimumab
    - Infliximab
    - Ixekizumab
    - Rituximab

- Sarilumab
- Secukinumab
- Tocilizumab
- Ustekinumab

- History of bone marrow transplantation or solid organ transplant.
- Known history of Hepatitis B or Hepatitis C.
- Known history of mycobacterium tuberculosis infection at risk for reactivation.
- Known history of gastrointestinal perforation or active diverticulitis.
- Multi-organ failure as determined by primary treating team
- Any other documented serious, active infection besides COVID-19.
- Pregnant patients and nursing mothers
- Patients who are unable to discontinue scheduled antipyretic medications, either as monotherapy (e.g., acetaminophen or ibuprofen [aspirin is acceptable]) or as part of combination therapy (e.g., hydrocodone/acetaminophen, aspirin/acetaminophen/caffeine [Excedrin®])
- CRP < 40 mg/L (or ug/mL)

3.4 Assignment of eligible patients to Group A or Group B

Patients will be assigned to Group A if:

- C-reactive protein (CRP) ≥ 75 ug/mL

AND

Any one of the following criteria are met:

- Previous ICU admission
- Previous non-elective intubation
- Admission for heart failure exacerbation within the past 12 months
- History of percutaneous coronary intervention (PCI)
- History of coronary artery bypass graft (CABG) surgery
- History of cerebrovascular accident with residual, patient-reported neurologic deficit
- Diagnosis of pulmonary hypertension
- Baseline requirement for supplemental O_2
- Diagnosis of interstitial lung disease (ILD)
- Admission for chronic obstructive pulmonary disease (COPD) exacerbation within the past 12 months
- Asthma with use of daily inhaled corticosteroid
- History of pneumonectomy or lobectomy
- History of radiation therapy to the lung
- History of HIV
- Cancer of any stage and receiving active treatment (excluding hormonal therapy)
- Any history of diagnosed immunodeficiency
- End-stage renal disease (ESRD) requiring peritoneal or hemodialysis
- BMI >30 kg/m^2

- Baseline supplemental oxygen required (in 24hrs prior to first tocilizumab dose) >6L/min Nasal cannula

All other patients meeting study eligibility criteria will be assigned to Group B.

3.5 Gender, Age, Racial and Ethnic Origin of Subjects

Men and women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION AND DATA COLLECTION/MANAGEMENT

4.1 General Guidelines

Patients will be identified as potential participants in this clinical trial through medical record screening and collaboration with the COVID-19 clinical team. Primary teams and Emergency Department teams will be encouraged to send the medical record numbers of potentially eligible patients to investigators (PDR, GWS, BH) using the UCM secure paging system (Spok). Information sheets will be posted in Internal Medicine team rooms and in strategic locations of the Emergency Department (determined by DB) for nurses and physicians.

Before any study-specific evaluations are performed, all patients must have given written informed consent for the study. Patients must meet all of the eligibility requirements listed in Section 3.0. Eligible patients will be entered on study by the University of Chicago into a REDCap database used for both registration and data collection (28).

An investigator will confirm eligibility criteria and the informed consent process and a member of the study team will complete the registration case report form.

4.2 Informed Consent Process

Given the unique nature of the COVID-19 pandemic and the risk for transmission to health care and research staff, we will obtain informed consent from possible participants by the following process:

1. Prospective study participants/representatives identified by an investigator will receive two (physical) copies of the written informed consent form (ICF) for their review from the research team, to be delivered by unit staff caring for the patient. ICFs delivered for review will have been signed by an investigator. A patient's representative may alternatively be provided a link to the consent in RedCap.
2. Phone or video conference will be scheduled between a member of the research team and the prospective study participant/representative. Research team and prospective study participant/representative will discuss the ICF and intent of the study as well as risks/benefits to participation. This conversation will be witnessed by the unit staff caring for the prospective participant/representative.

3. If the prospective study participant/representative understands the risks/benefits of the study and is interested in participating, study participant or his/her designated representative will sign both copies of the ICF. The witness will sign both copies of the ICF. If the consent is delivered through RedCap, this signature process happens electronically within the RedCap system.
4. The research staff will document the informed consent conversation in the electronic medical record as a Telephone Encounter note in parallel with the conversation in an Epic Telephone Encounter created for the purposes of research. A standard note form (dot-phrase) will be used for all study participants (Appendix A).
5. At this time, two fully executed ICFs will exist. The study participant/representative will keep one of them in his/her possession as proof of a fully executed ICF. The other fully executed ICF will be bio-bagged in the patient's room and immediately bio-bagged once more upon exit and will be kept for filing by research staff. If the consent process occurred electronically, then the fully executed consent will be an electronic file PDF/RedCap document.

4.3 **Exemption from Investigational New Drug Application**

Investigational New Drug (IND) is not required at this time, on the basis of September 2013 Food and Drug Administration Guidance (29), section IV.A. This study meets all conditions set forth:

- It studies a drug product, tocilizumab, legally marketed in the United States.
- The intent of the study is *not* to report to FDA a well-controlled study in support of label change.
- The intent of the study is *not* to support a change in marketing practices.
- This study focuses on the COVID-19 patient population who have been admitted to the hospital. The mortality for COVID-19 among inpatients is quoted as greater than 25% (1). Though it is a new clinical situation in which to study tocilizumab, it is *not* prohibitively high-risk. Moreover, it does not represent a prohibitively large increase in risk over the baseline risk faced by this unique and ill patient population. Despite the presence of the global COVID-19 pandemic, tocilizumab continues to be administered at doses nearly an order of magnitude higher than the doses proposed in this study to patients with rheumatologic conditions such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis. If the risk/benefit calculus of the practice of continuing high-dose tocilizumab is acceptable at this time, then this study, with its comparable risk/benefit calculus, is as well. Furthermore, an emerging standard of care in critical COVID-19 disease is the use of tocilizumab at a dose significantly higher than the dose proposed in this study.
- The study will be reviewed and conducted under the jurisdiction of an Institutional Review Board in accordance with 21 CFR part 56 and will have informed consent as described below, in accordance with 21 CFR part 50.
- The study is *not* intended to promote or commercialize tocilizumab.

4.4 **Registration Process**

To complete the registration process, a member of it the study team will:

1.) Assign the patient a study number (e.g. patient would be UC-001)
2.) Register the patient on study
3.) Collect pre-treatment laboratory studies as below
4.) Assign study participant to Group A or Group B.

When registering a subject, the following must occur:

- The patient must have signed the consent form.
- The date the patient is registered will be considered the patient's "On Study Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by REDCap on this date.

The University of Chicago will maintain a secure, password protected, and regularly backed up REDCap clinical trials database. All data will be entered into the REDCap database. Data will be stored in RedCap using the patient-study number.

4.5 **Data to Collect**

The following baseline clinical variables will be collected and recorded on the Eligibility and Registration Form:

- Age
- Sex
- Race
- Complete medical history

The following laboratory data collected within 24 hours of tocilizumab will be reviewed by investigators:

- Complete blood count (CBC) with automated differential (followed by manual differentiation as dictated per UCM clinical protocols)
- Basic metabolic panel (BMP)
- Liver function tests (LFT)
- D-dimer
- Fibrinogen
- Lactic dehydrogenase (LDH)
- C-reactive protein (CRP)
- Westergren sedimentation rate (ESR)
- Ferritin
- Cytokine panel/IL-6
- Triglycerides

Patients will have the following laboratory studies performed in the 6 hours prior to administration of tocilizumab and at the time of tocilizumab dosing if more than 2 hours prior to the administration of the tocilizumab:

CRP

In line with emerging standard of care clinical management of COVID-19 patients at UCM, investigators will review the results of the following laboratory studies, performed at 24-hour intervals during the patient's hospitalization (or with clinical decompensation):

- Complete blood count (CBC) with automated differential (followed by manual differentiation as dictated per UCM clinical protocols)
- BMP
- LFT
- CRP

Investigators advise but do not require the following laboratory and imaging studies be performed to monitor clinically:

Laboratory studies performed at 24-hour intervals during the patient's hospitalization (or with change in clinical status):

- ESR
- Ferritin

Laboratory studies performed at 48-hour intervals during the patient's hospitalization (or with change in clinical status):

- D-dimer
- Fibrinogen
- LDH
- Triglycerides

Laboratory study performed 120 hours after tocilizumab administration:

- Cytokine panel

Imaging study performed 24, 72, and 120 hours (+/- 6 hours for each) following administration of tocilizumab (or with change in clinical status):

- CXR (portable single-view is acceptable), or
- CT chest

The details of these results will be recorded on the Imaging Form.

All labs and tocilizumab doses while inpatient will be collected on the Labs and Tocilizumab Administration Form. If the patient has a change in clinical status requiring the use of invasive mechanical ventilation, initiation of vasopressor support, or (for patients *not* requiring non-invasive mechanical ventilation upon admission) the use of non-invasive mechanical ventilation, please record labs on the Patient Change in Clinical Status Labs Form. If the patient goes to the ICU and is subsequently transferred out, please complete a second Patient Change in Clinical Status Labs Form.

For every dose of tocilizumab administered, please record the details (dose amount, date, time, etc.) on the Labs and Tocilizumab Administration Form.

When a patient is in follow-up, they will be followed for survival for 28 days following the first dose of tocilizumab or hospital discharge, whichever occurs latest. The details will be recorded on the Follow-Up Form.

4.6 Data Submission

All forms collected for the trial will be entered into the REDCap database.

5 DRUG ADMINISTRATION

Treatment will be administered to the patient while they are admitted to a University of Chicago Medicine. Tocilizumab is commercially available and will not be provided by the study.

Therapy will consist of tocilizumab administered at doses determined by the Principal Investigator, as based on the most recent Operating Committee meeting. For the initial patients (i.e., prior to the first Operating Committee meeting), doses of 200 mg (Group A) and 80 mg (Group B) will be utilized, as discussed in section 1.2.4.

The study Operating Committee (discussed in 5.2) will guide subsequent enrollment and dosing decisions in response to local constraints such as medication supply. We anticipate initial enrollment of five patients each in both Groups A and B in the first two weeks of the study.

5.1 Duration of Treatment

Patients will be considered for a total of 2 doses of tocilizumab. Participants will be followed up evaluation of re-dosing 24-48 hours after first tocilizumab dose. Patients will be considered for re-dosing of tocilizumab if they meet one or more of the clinical criteria *and* the biochemical criteria below:

- Clinical criteria
    - Increased maximum supplemental oxygen required over approximately 24 hours following the first tocilizumab dose compared to pre-dosing or baseline supplemental oxygen requirements *and* determined to be associated with COVID19 pneumonitis as determined by primary team *or*
    - Increased maximum temperature over approximately 24 hours following the first tocilizumab dose compared to maximum temperature in the 24 hours prior to first tocilizumab administration

AND

- Biochemical criteria
    - CRP decrease of <25% of baseline CRP and >40mg/L:

- This follow-up CRP will be measured >=24 hours post first tocilizumab dose and >=24 hours since the draw of the CRP within 2 hours of first dose administration.
- Baseline CRP
  - If pre-drug CRP was within 2 hours prior to first tocilizumab administration, this will be the baseline CRP
  - If pre-drug CRP was within 2-6 hours prior to first tocilizumab administration and a repeat CRP was ordered at the time of ordering tocilizumab, the baseline CRP will be the higher of these two values

Re-dose if meets both clinical *and* biochemical parameters met:	
1. Patient would meet **clinical** parameter if	Follow-up-Tmax* > Pre-TCZ Tmax *or* Follow-up-O2-required* > Pre-TCZ O2 required
2. Patient would meet **biochemical** parameter if	Follow-up- CRP[†]>40mg/L *and* Follow-up CRP[†] decrease is <25% of Baseline CRP[#]

*Max in 24hours *post*TCZ compared to Max value in 24hours *pre*TCZ and associated with COVID19 per primary team
[†]Follow up CRP will be >= 24 hours after first tocilizumab dose *and* >=24 hours after baseline CRP
[#]Baseline CRP will be defined according to when results in reference to drug administration as follows:
- If pre-drug CRP was within 2 hours prior to first tocilizumab administration, this will be the baseline CRP
- If pre-drug CRP was within 2-6 hours prior to first tocilizumab administration and a repeat CRP was ordered at the time of ordering tocilizumab, the baseline CRP will be the higher of these two values

5.2 Duration of Study

Therapy with tocilizumab will continue unless one of the following events occurs:

1. Severe allergic or infusion reaction occurs
2. Treating physician determination that the risks or downsides of tocilizumab administration outweigh the potential benefits.
3. Patient withdraws consent.
4. Patient is withdrawn from the study at the discretion of the investigator or the patient's attending physician.

Note: Patients will be followed for overall survival for 28 days after tocilizumab administration or liberation from mechanical ventilation, whichever occurs latest.

5.3 Study Operating Committee

To account for the constantly changing conditions caused by the COVID-19 pandemic, with resultant expectation of drug shortage, and the possibility of unexpected results in

provisioning tocilizumab to COVID-19 patients despite sound biologic and mechanistic rationale, we propose a study Operating Committee to guide governance and conduct of this study.

The primary role of this committee is to discuss study progress and determine specifics for next steps in the study. These are expected to include questions of study continuation, enrollment in the next cohort, and dosing decisions. Prior to initiation of the study, the Operating Committee agrees to be bound by certain parameters:

- Size of next cohort
- Possible increases in doses, which will not increase from one cohort to the next by more than 100%
- Possible decreases in doses, which will generally not decrease from one cohort to the next by more than 50%

The voting members of the Operating Committee will be Drs. Reid, Pisano, Ratain, and Strek, with all decisions requiring unanimous consent, including enrollment beyond the initial 5 patients in each Group. All other study investigators will be non-voting members of the Operating Committee. Additional expert consultation will be requested on an as needed basis, at which point expert consultants will be *ex officio*, non-voting members of the Operating Committee. The first Operating Committee meeting will occur no later than 14 days from the first patient and thereafter at least every two weeks (and likely more frequently). It is mandatory for voting members to be present each time the Operating Committee convenes, as a 100% consensus is needed from the voting members before a decision is implemented into the next steps for the study.

The Operating Committee will also be tasked with making decisions about the success or failure of a given dose level within a study cohort. The Committee will be guided by the performance of the drug in the previously discussed strategy (Figure 5). Success will be defined by a low rate of re-dosing and high rate of clinical and biochemical resolution. Metrics will be assessed by the Operating Committee and whatever consultants deemed necessary. Decisions will require unanimous consent among the Operating Committee's voting members.

Further enrollment decisions will be made by the trial's Operating Committee. Further enrollment will be determined by the Operating Committee by unanimous consent of the voting members.

The Operating Committee will assess the most up-to-date clinical information for each of the enrolled patient and also have the task of altering stratification criteria between group A and group B as well as redosing parameters as study continues, only via unanimous vote by the voting members and without any dissension from non-voting members. This is to ensure the utmost safety of the patient by being able to enact on evaluation of patient's hospital courses in real time: allocate patients in appropriate drug dosing group (group A versus group B) *and* avoid inappropriate redosing.

6 STUDY ASSESSMENTS

6.1 Pretreatment Evaluation

Investigators will review the following studies, collected within 24 hours prior to treatment with the first dose of tocilizumab as part of routine clinical care:

- Complete blood count (CBC) with automated differential (followed by manual differentiation as dictated per UCM clinical protocols)
- Basic metabolic panel (BMP)
- Liver function tests (LFT)
- D-dimer
- Fibrinogen
- Lactic dehydrogenase (LDH)
- C-reactive protein (CRP)
- Westergren sedimentation rate (ESR)
- Ferritin
- Cytokine panel/IL-6
- Triglycerides
- 12-lead EKG

Patients will have the following laboratory studies performed in the 6 hours prior to administration of tocilizumab and at the time of tocilizumab dosing if more than 2 hours prior to the administration of the tocilizumab:

CRP

Within 12 hours prior to treatment with the first dose of tocilizumab administration, the patient will have had a chest radiograph (CXR) (portable single-view is acceptable) or computed tomography (CT) of chest performed.

6.2 On-Study Evaluation

On-study evaluation refers to measurement of vital signs and laboratory studies before and after a patient has received tocilizumab. Subjects will be monitored during and following the drug infusion to monitor for any complications or reactions. As part of routine care, subjects will be seen daily while in the hospital and will be monitored through blood tests for general health as well as liver function. Vital signs will be monitored daily while in the hospital, physical exams, assessment of COVID infection, and CT scans or chest x-rays as necessary for routine care.

Patients will have the following laboratory studies performed in the 6 hours prior to administration of tocilizumab and at the time of tocilizumab dosing if more than 2 hours prior to the administration of the tocilizumab:

CRP

Investigators will review the results of the following laboratory studies, performed at 24-hour intervals during the patient's hospitalization (or with clinical decompensation):

- CRP

Other laboratory studies collected as part of the routine clinical care of COVID-19 patients, as determined by institutional standards and the UCM COVID-19 Working Group, will be monitored by investigators, as well.

6.3 Collection and Handling of Specimens:

Clinical labs will be drawn and processed normally as per standard of care.

6.4 Off Study Assessments

Enrolled patients will be followed throughout their hospital course, and for survival for 28 days after receiving the first dose of tocilizumab.

6.5 Study Calendar

6.5.1 Overall Study Calendar

	Baseline standard of care labs[a]	Regist-ration	Standard of care labs collected prior to administration of tocilizumab	Standard of care lab assessments every 24 hours after tocilizumab	Labs we advise but do not require every 48 hours after tocilizumab	Patient Intubated **OR** Patient transferred to ICU **OR** Patient change in clinical status	Patient Extubated **OR** Patient transferred from ICU	Follow Up Period 28 Days from Drug Administration
Written Informed Consent	X							
Lab set 1[b]	X		X					
Lab set 2[c]	X			X		X	X	
Lab set 3[d]	X				X	X	X	
Imaging[e]	X			X[e]		X	X	
Eligibility Confirmation	X	X						
Survival Follow Up								X

[a] In addition to the baseline labs, standard of care 12-lead EKG and cytokine panel/IL-6 will be obtained.
[b] CRP Lab to be collected by the primary team within 6 hours (and at time of drug administration if 2-4 hours prior to tocilizumab administration) prior to and/or at the time of tocilizumab administration
[c] Standard of care labs to be collected by the primary team every 24 hours or if there is a change in clinical status of patient are CBC, BMP, LFT, and CRP. Investigators advise ESR and ferritin.
[d] Labs advised to be collected by the primary team every 48 hours or if there is a change in clinical status of patient are D-dimer, fibrinogen, LDH, and triglycerides.
[e] Likely standard of care imaging will consist of CXR or CT chest. For baseline assessment, imaging study should be completed within 12 hours of initial tocilizumab administration. Imaging that may occur as part of standard of care (advised by investigators) at 24, 72, and 120 hours following tocilizumab.
Note: Investigators advise a cytokine panel performed at 120 hours after tocilizumab administration.

7 SAFETY

7.1 Risks

Tocilizumab is a commercially available drug approved for the treatment of diseases other than COVID-19. To date, there is no prospective, randomized controlled trial data

suggesting tocilizumab's efficacy in COVID-19. There is no standard dose of tocilizumab for COVID-19. The FDA-labeled dose of tocilizumab for CRS is 8 mg/kg. In comparing a standard of care dose to reduced dose, there is a risk that the reduced dose will lead to poorer clinical outcomes for patients. Patients will be informed of this possibility. Patients assigned to low-dose tocilizumab blocks may receive an additional dose of tocilizumab if there is no evidence of clinical or biochemical improvement.

Side effects and theoretical risks associated with tocilizumab include:

- Serious infection
- Gastrointestinal perforation
- Hypersensitivity reaction, including anaphylaxis and death
- Immunosuppression and increased risk for secondary infection (urinary tract infection, bacterial pneumonia, cellulitis, herpes zoster, gastrointestinal infection, diverticulitis, septic arthritis, and, rarely, opportunistic infections)
- Neutropenia
- Thrombocytopenia
- Elevated liver enzymes
- Elevated lipids
- Immunogenicity (development of antibodies against tocilizumab)
- Hepatitis B virus reactivation
- Rarely, nervous system problems such as multiple sclerosis.
- Tocilizumab may increase your risk of cancer
- Tocilizumab may harm unborn or nursing babies

Theoretical risks associated with tocilizumab in the context of COVID-19 infection include:

- Suppression of innate antiviral immunity, resulting in progression of COVID-19 disease

8 MEASUREMENT OF EFFECT

8.1 Clinical Response – Response in Maximum Temperature (Tmax)

Tmax Response. Maximum temperature within 24-hour period of time (0:00-23:59) on the day prior to, day of, and every 24 hours after tocilizumab administration. The primary endpoint is absence of Tmax greater than or equal to 38ºC in the 24-hour period following tocilizumab administration.

8.2 Biochemical Response - C-reactive protein Response

Time to CRP normalization. Calculated as the number of hours between tocilizumab administration and first normal CRP value.

Rate of patients whose CRP normalize. Calculated as the ratio of the number of patients who achieve normal CRP value following tocilizumab administration and total number of patients who receive tocilizumab.

8.3 **28-Day Overall Survival**

28-Day Overall Survival is defined as the status of the patient at the end of 28 days starting from the time of the first dose of tocilizumab.

8.4 **Survival to Hospital Discharge**

This will be defined as the percentage of patients who are discharged in stable condition compared to the percentage of patients who die in the hospital. Patients who are discharged to hospice will be excluded from this calculation.

8.5 **Progression of COVID-19 Pneumonitis**

This will be a binary outcome defined by worsening COVID-19 pneumonitis resulting in transition from Group A or Group B to critical COVID-19 pneumonitis during the course of the patient's COVID-19 infection.

8.6 **Rate of Non-elective Mechanical Ventilation**

This will be a binary outcome defined as worsening COVID-19 disease resulting in the use of non-invasive (BiPap, heated high-flow nasal cannula) or invasive positive pressure ventilation during the course of the patient's COVID-19 infection. For patients admitted to the hospital using non-invasive mechanical ventilation, the utilization of mechanical ventilation will count toward this metric, as well.

8.7 **Duration of mechanical ventilation**

This will be a continuous outcome defined by the amount of time between initiation and cessation of mechanical ventilation (invasive and non-invasive).

8.8 **Time to Mechanical ventilation**

This will be a continuous outcome defined by the amount of time between tocilizumab dose administration and the initiation of mechanical ventilation. This will be treated as a time-to-event with possible censoring.

8.9 **Rate of Vasopressor or Inotropic Medication Utilization**

This will be a binary outcome defined as utilization of any vasopressor or inotropic medication.

8.10 **Duration of Vasopressor of Inotropic Medication utilization**

This will be a continuous outcome defined by the amount of time between initiation of first and cessation of last vasopressor medications.

8.11 Time to Vasopressor or Inotropic Utilization

This will be a continuous outcome defined by the amount of time between initiation of first and cessation of last vasopressor medications. This will be treated as a time-to-event with possible censoring.

8.12 Number of ICU Days

Number of ICU days is defined as the time period when a patient is admitted to the ICU (defined as the timestamp on the first vital signs collected in an ICU) until they are transferred from the ICU to a non-ICU setting such as a general acute care bed (defined as the timestamp on the first vital signs collected outside an ICU, excepting any "off the floor" vital signs charted from operating rooms or procedure or imaging suites). Death in the ICU will be a competing risk.

8.13 Duration of Increased Supplemental Oxygen Requirement from Baseline

This will be an ordinal outcome defined by the number of days over which the participant requires supplemental oxygen in excess over his/her baseline supplemental oxygen requirement. The supplemental oxygen requirement is defined as the highest liters-per-minute flow of supplemental oxygen required by the patient each day over the course of the hospitalization.

9 STATISTICAL PLAN AND CONSIDERATIONS (10)

9.1 Sample Size Determination

The sample size is not formally determined at this time. Given expected constraints related to the COVID-19 epidemic, it is unclear whether drug shortages will limit enrollment and provisioning of tocilizumab. Continued enrollment in the context of drug shortages will be determined by the Operating Committee.

9.2 Definition of Evaluable Patients

Patients are considered eligible for analysis if they have enrolled in the study and received at least one dose of tocilizumab.

9.3 Statistical Methods

Primary endpoints will be Tmax response (<38°C), time to CRP normalization, and rate of patients whose CRP normalize in the study population.

Secondary endpoints including overall survival and survival to hospital discharge, which will be calculated by the Kaplan-Meier (26) method and compared between groups using a log-rank test. Rate of progression of COVID-19 pneumonitis, rate of non-elective

mechanical ventilation, number of days to mechanical ventilation (invasive and non-invasive), number of days requiring mechanical ventilation, rate of vasopressor support utilization, number of days to vasopressor support, number of days of vasopressor support, and ICU time in non-critically ill patients with COVID-19 pneumonitis who are treated with tocilizumab will be assessed using descriptive and nonparametric statistics.

10 STUDY MANAGEMENT AND REGULATORY AFFAIRS

10.1 Institutional Review Board (IRB) approval

The investigator will obtain, from the University of Chicago Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Chicago IRB of the deviation.

The University of Chicago IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP) (30).

10.2 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on GCP; and relevant policies, requirements, and regulations of the University of Chicago IRB, University of Chicago and UCMC, State of Illinois, and applicable federal agencies.

10.3 Informed Consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor-investigator, will obtain the written, signed informed consent of each subject, prior to performing any study-specific procedures on the subject. The date and time that the subject signs the informed consent form will be recorded. The -investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the sponsor-investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

10.4 **Amendments to the Protocol**

All modifications to the protocol or consent form will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol.

10.5 **Annual IRB Renewals, Continuing Review and Final Reports**

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

10.6 **Record Retention**

Study documentation includes all case report forms (CRFs), data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

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Appendix A: Informed Consent Documentation: Telephone Note Template

NB: '***' is an optional field. Either the prospective participant of his/her designated representative's name will be listed in the body of the text. "@NAME@" refers to the name of the patient. "@HIS@" refers to smartphrase use of "his" or "her" in the document. "@HE" refers to smartphrase use of "he" or "she" in the document. "@TODAYDATE@" refers to smartphrase use of the date on which the note was drafted.

Informed Consent Documentation for IRB *
Investigating the role of tocilizumab in the prevention of clinical decompensation in non-critically ill patients hospitalized with COVID-19 pneumonitis

Name: @NAME@
Member of Research Team Obtaining Informed Consent: @ME@

I discussed the above-referenced research study with @NAME@ *** @HIS@ designated representative ***
via telephone/videoconference on @TODAYDATE@. @NAME@ *** @HIS@ designated representative *** exhibited understanding of the research study and its risks/benefits.

We assured the patient that @HE@ is free to withdraw from the study at any time. All questions were answered to the patient's satisfaction.

After consideration of the risks/benefits, @NAME@ *** @HIS@ designated representative *** provided written informed consent as well as verbal consent to participate in the study. Written informed consent was provided on @TODAYDATE@ at ***:***. The presence of a physical signature was confirmed with the patient's bedside nurse.

The signed informed consent form will be scanned and uploaded to the Media tab of Epic. A copy of this note and the signed informed consent form (together comprising a fully executed informed consent document) will be provided to @NAME@ *** @HIS@ designated representative ***.

Garth W Strohbehn MD MPhil
Fellow, Hematology/Oncology

on behalf of the research team for IRB ***
"Investigating the role of tocilizumab in the prevention of clinical decompensation in non-critically ill patients hospitalized with COVID-19 pneumonitis"