Study Title: COVID-OUT: Outpatient Treatment for SARS-CoV-2 infection, a Factorial Randomized Clinical Trial
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Version Date of Protocol: 08 December 2021

PROTOCOL COVER PAGE

Protocol Title	COVID-OUT: Outpatient Treatment for SARS-CoV-2 infection, a Factorial Randomized Clinical Trial
Protocol Number	MET29324
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VERSION HISTORY

Version #	Version Date	Summary of Changes
1.0	08DEC2020	Initial protocol
2.0	28 Feb 2021	Protocol amendment submitted to allow screening online.
3.0	08MAR2021	Protocol amendment: response to administrative clarification of request to remove Post-exposure prophylaxis and added final factorial design.
3.1	30APR2021	Includes response to FDA questions on full factorial design.
3.2	08July2021	Small updates, mostly around data collection
3.3	02 Sept 2021	Small update around Inclusion criteria
3.4	08 Dec 2021	Updated sample size.

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ABBREVIATIONS/DEFINITIONS

- ACE2 Angiotensin-Converting Enzyme
- AE Adverse Events
- AHC-IE Academic Health Center Information Exchange
- ARDS Acute Respiratory Distress Syndrome
- COVID-19 Disease caused by the virus SARS-CoV-2, or "Wuhan coronavirus"
- CLIA Clinical Laboratory Improvement Amendments
- CTSI Clinical and Translational Science Institute
- DM Type 2 Diabetes Mellitus
- DSMB Data Safety Monitoring Board
- ECMO Extracorporeal membrane oxygenation
- eConsent Electronic consent
- ED Emergency Department
- EGFR Estimated Glomerular Filtration Rate
- EHR Electronic Health Record
- ER Extended Release
- GDF 15 Growth/Differentiating Factor 15
- ICF Informed Consent Form
- ICU Intensive care unit
- IDS Investigational Drug Services
- IL-6 Interleukin 6
- IL-10 Interleukin 10
- IQR Interquartile Range
- IR Immediate Release
- MHealth University of Minnesota Health
- mtDNA Mitochondrial DNA
- mTOR Mammalian Target of Rapamycin
- NDMA Nitrosodimethylamine
- NETs Neutrophil-Extracellular Traps
- RC's Research Coordinators, and refers to members of the study team (includes project manager, Co-I, PI).
- SAE Severe Adverse Event
- SARS Severe Acute Respiratory Syndrome
- SOPs Standard Operating Procedures
- SIREN Strategies to Innovate Clinical Trials network
- TLR7 Toll-Like-Receptor 7
- TNF-alpha Tumor Necrosis Factor alpha
- UMMC University of Minnesota Medical Center

1.0 Objectives

1.1 Title:

COVID-OUT: Outpatient treatment of SARS-CoV-2 infection, a factorial Randomized Clinical Trial.

Purpose:

1) To understand whether metformin vs fluvoxamine vs ivermectin vs metformin+fluvoxamine vs metformin+ivermectin are superior to placebo in non-hospitalized adults with SARS-CoV-2 infection for preventing COVID-19 disease progression.
2) To understand if the active treatment arms are superior to placebo in improving viral load, serologic markers associated with Covid-19, and gut microbiome in non-hospitalized adults with SARS-CoV-2 infection.
3) To understand if any of the active treatment arms prevent long-covid syndrome, PASC (post-acute sequelae of SARS-CoV-2 infection).

2.0 Background

2.1 Significance of Research Question/Purpose:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rapidly spreading viral infection causing COVID-19 disease. While vaccine development for SARS-CoV-2 has been promising, there may be hurdles to wide distribution, reduced immunity in persons with advanced age or obesity (a state of thymic aging), and reduced willingness among the public to receive a vaccine developed so quickly.[1] Additionally, new strains appear resistant to the vaccines.

2.2 Preliminary Data:

Several observational studies have shown an association with decreased mortality with outpatient metformin use in patients who were then hospitalized with COVID-19, including a study we conducted.[2] Two prospective studies have found efficacy of fluvoxamine in prevention hospitalization and death.[3,4] Biophysical modeling of the SARS-CoV-2 life cycle, which accurately predicted the efficacy of remdesivir and the lack of efficacy of hydroxychloroquine, identified viral protein translation, which is inhibited by mTOR inhibitors such as metformin, as an especially sensitive node in the model (Castle et al., 2020).

2.3 Existing Literature:

Table 1: Existing Literature

Papers in 2020 with observational mortality findings related to metformin and COVID-19.			
Author	**Population**	**Methods**	**Finding**
Luo et al.[1] *Am J Trop Med Hyg*	283 adults with DM hospitalized with COVID-19 in Wuhan.	Retrospective review, appears to be of home metformin us; 104 in metformin, 179 in no-metformin group	**Hospital mortality 2.9% in metformin group vs 12.3% in no-metformin group, p=0.01.** OR for survival: 4.36 (1.22-15.59, p=0.02). No difference in length of stay. No mortality difference based on use of other DM medications.

Cariou et al,[2] "Coronado study" *Diabetalgia*	1,317 adults with DM in France, with or without home metformin use	Multi-center observational study. Main outcome: mortality or intubation; Secondary outcome was mortality.	HbA1C was not associated with main outcome (p=0.28) or death (p=0.91); **home metformin was associated with lower mortality OR 0.59 (0.42, 0.84).** Increased risk of death with insulin OR 1.71, (1.20, 2.43). No association with other DM meds.
Bramante et al. *Lancet Healthy Longevity.*	6,256 adults with DM or obesity hospitalized for COVID-19 in the US.	Retrospective review of USA UHG claims data of home metformin use (claims for >= 90 days in prior 12 months)	Metformin was associated with a reduced mortality in females: **OR 0.759 (0.601, 0.960)** by propensity matching; **OR 0.780 (0.631, 0.965)** by a mixed effects model; **OR 0.785 (0.650, 0.951)** by Cox proportional-hazards.
Crouse et al. *Metrxiv.org*	239 persons with diabetes and COVID-19	Retrospective review of 25,326 subjects tested for COVID-19 between 2/25 - 6/22/20 at UAB.	- Metformin treatment was independently associated with a significant mortality reduction in subjects with diabetes and COVID-19, OR 0.33 (0.13-0.84; p=0.02)
Paper with laboratory findings suggesting lower IL-6 in metformin users with COVID-19			
Chen et al.[3] *Diabetes Care*	904 patients with COVID-19, 136 of whom had DM	Retrospective review of patients with DM and COVID-19 in association with glucose lowering medications.	Metformin users had lower IL-6 (4.07 vs 11.1, p=0.02). In PCR-confirmed cases, IL-6 was also lower in metformin users than non-metformin users (4.77 vs 11.1, p=0.024). No differences between DDP-4 users vs non-users. GLP-1 use not reported.

Bramante et al, *under review.*	2,135 patients with SARS Co-V-2, subset with lab values	Lab Bicarb Lactate IL-6 CRP	No Metformin 25 (8), n=438 1.5 (1.1), n=136 1,702 (1,011), n=66 111 (83), n=290	Metformin 26 (5), n=25 1.3 (0.5), n=7 54 (69), n=7 84 (75), n=16	P Value 0.38 0.78 0.08 0.02

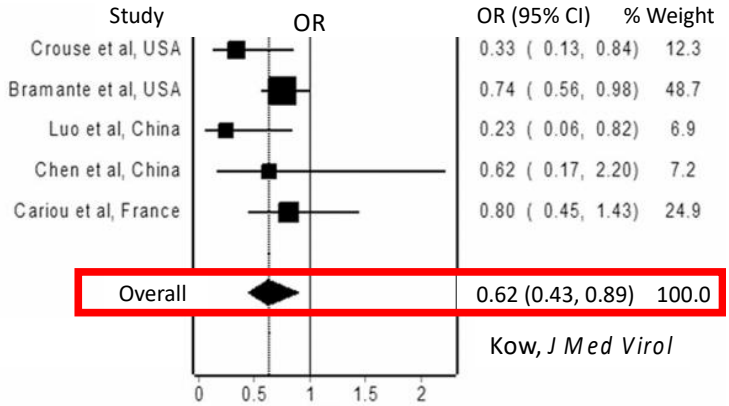


Figure 1: Pooled risk of mortality in hospitalized COVID-19 patients with diabetes with preadmission metformin. (heterogeneity: I2= 29%; p = .23).[5]

Prior to COVID-19, the exact mechanisms by which metformin conveyed benefit was a matter of debate. There are several ways by which metformin may offer protection from SARS-CoV2.

Existing Literature on Mechanistic Reasons for Metformin to be Effective against COVID:

High glucose is associated with worse COVID-19 outcomes: Metformin reduces blood glucose levels, but not below physiologic levels, by reducing hepatic gluconeogenesis. Worse glucose control has also been associated with higher mortality and end-organ complications in patients with COVID-19.[6]

Metformin could decrease endothelial injury and its complications: Metformin has been shown to improve microvascular endothelial function in women perhaps due to a significant increase in response to acetylcholine, decrease in insulin resistance, and non-significant decrease in tissue plasminogen activating factor, as was shown in a randomized control study of 8 weeks of metformin versus placebo in women with angina and normal coronary arteries .[7] Pulmonary vascular endotheliatis has been observed in the lungs of patients with COVID-19.[8] Endothelial dysfunction may be an important mechanism and therapeutic target in mitigating COVID-19 sequelae. Metformin decreases thrombosis in long-term follow-up, possibly by inhibiting platelet activation factor and mitochondrial DNA (mtDNA) release,[9,10] and may mediate improved cardiovascular outcomes via mechanisms beyond glucose control. COVID associated coagulopathy and thrombosis is a unique attribute to this disease, and the pathophysiology is poorly understood. Further, frequently widespread micro and macrovascular thrombosis has been reported in autopsies of patients with COVID 19.[11,12]

Metformin decreases neutrophil-extracellular traps (NETs), and the neutrophil to lymphocyte ratio.[13-15] NETs are microbiocidal compounds containing DNA, histones, and proteins.[14,15] Sera from patients with COVID-19 demonstrate elevated levels of these histones and DNA components.[15] It has been hypothesized that excessive NET formation leads to cytokine storm and microthrombus (possibly independent of tissue factor), and ultimately acute respiratory distress syndrome (ARDS) in COVID-19.[16] Lymphopenia and neutrophil infiltration in pulmonary capillaries have been an important feature of severe COVID-19 disease.[13,17-19] Metformin's inhibition of NET release could therefore mitigate the development of downstream lung injury.

Metformin could decrease the viral cycle: There is evidence that metformin increases endosomal pH via action on vacuolar ATPase and/or endosomal Na+/H+ exchangers,[20] thus reducing viral replication. Metformin leads indirectly to alteration of the mammalian target of rapamycin (mTOR) pathway,[21] which could decrease the viral lifecycle through effects on proteins including Orf9c and Nsp7.[21] Biophysical modeling of the SARS-CoV-2 life cycle, which accurately predicted the efficacy of remdesivir and the lack of efficacy of hydroxychloroquine, identified viral protein translation, which is inhibited by mTOR inhibitors such as metformin, as an especially sensitive node in the model.[22] Metformin has been shown to inhibit mTOR, and mTOR inhibition is associated with efficacy against MERS and COVID-19.[23-25]

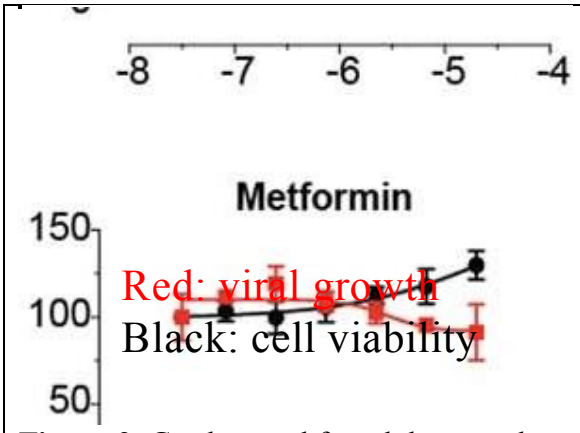


Figure 2. Gordon et al found decreased SARS-CoV-2 and increased cell viability with metformin in vitro.[21]

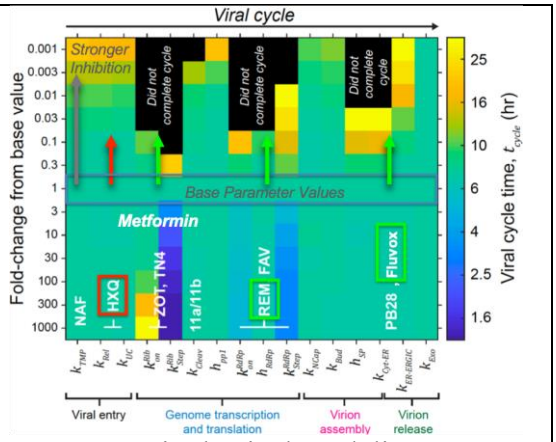


Figure 3. Biophysical modeling.

Metformin may decrease entry of SARS-CoV-2 into cells: Activation of AMPK by metformin increases expression of angiotensin-converting enzyme 2 (ACE2). Simultaneously, increased phosphorylation of the ACE2 receptor leads to conformational changes[26-28] that could theoretically decrease SARS-CoV-2 binding and entry into cells.[29]

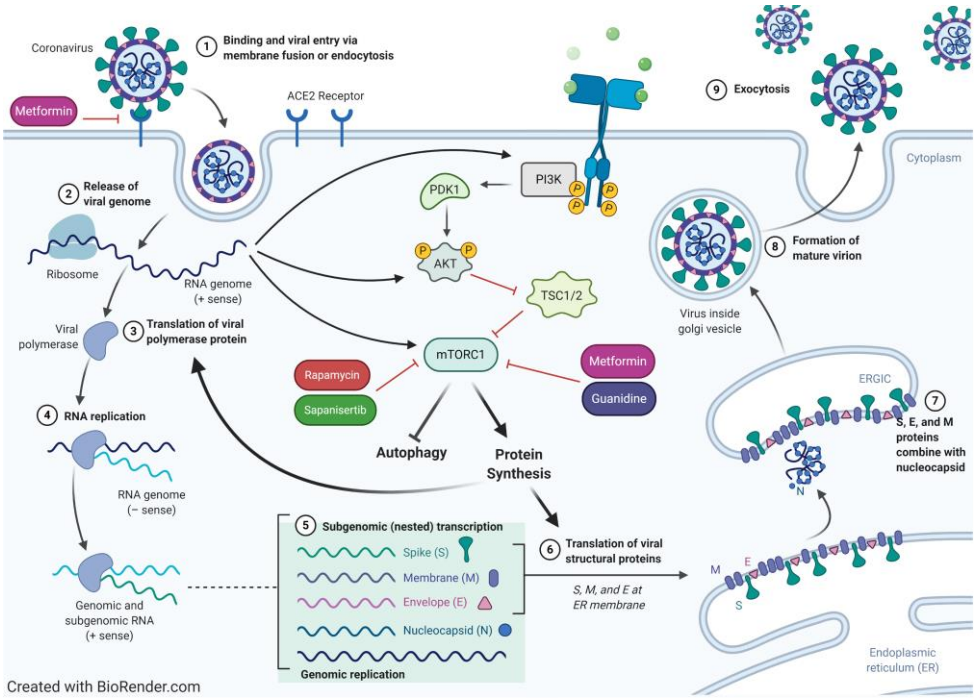


Figure 4, Karam et al, in press.

Metformin has immune-modulatory effects: In patients with and without diabetes, metformin has been shown to favorably alter inflammatory mediators, including interleukin 6 (IL-6), TNF-alpha, and to possibly boost interleukin 10 (IL-10), and suppress the C-C motif chemokine ligand.[13,30-32] Metformin's activation of the AMPK/mTor/Stat3 pathway seems to steer

macrophages away from the pro-inflammatory classical activation that produces TNF/IL6/IL1b, cytokines that contribute to morbidity in COVID-19.[33-35] Possible evidence of this effect was seen in a retrospective study by Chen et al of, review 904 patients with COVID-19 which showed that metformin users had lower IL-6 levels compared to non-metformin users (Table 2).[18] Metformin also inhibits toll-like-receptor 7 (TLR7) signaling and interferon production, which appears important to COVID-19 pathophysiology.[36,37] Metformin also inhibits IgE- and aryl hydrocarbon-mediated mast cell activation.[38] Mast cell activation has been implicated as an early indicator of inflammatory response to SARS-CoV-2. and possibly an indicator of impending cytokine storm.[39,40] Mast cells from female rats have been found to cause a greater increase in tumor necrosis factor alpha (TNF-alpha) than mast cells in male rats, which may explain the observational findings of reduced mortality in women on metformin, but no among men on metformin.[41]

Metformin has a history of anti-infectious properties: Metformin was found to have antiviral activity before SARS-CoV-2. In the 1940s and 1950s, metformin was used against influenza (as "Flunamine"), and was found to be effective against parainfluenza and cowpox.[42,43] Metformin has also been associated with improved response to anti-infectious agents in HIV and tuberculosis.[44] With the Zika virus, another RNA virus, activation of AMPK by metformin resulted in restricted viral replication by potentiating innate antiviral responses and decreasing glycolysis, with PKA Inhibitor PKI leading to decreased viral infection and replication.[45,46] In patients with hepatitis C, metformin has been associated with improved virologic response to antivirals through decreased insulin resistance.[47]

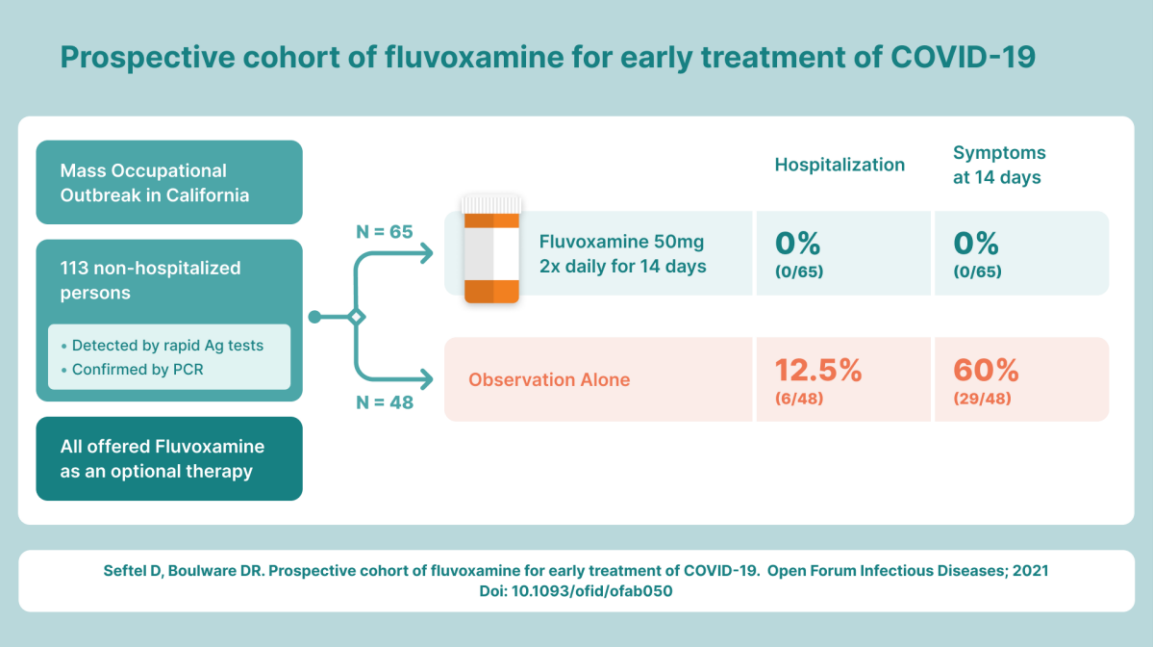
Metformin's past anti-infectious benefits have been both against the infectious agent directly, as well as by improving the underlying health of the human host. It is unknown if the lower mortality observed in patients infected with COVID-19 who are on metformin is due to direct activity against the virus itself, improved host substrate, or both.

Fluvoxamine

In addition to metformin, fluvoxamine appears to have important anti-viral and anti-inflammatory effects in SARS-CoV-2 infection. There is evidence that SARS-CoV-2 infection causes ER stress and activates pathways of unfolded protein response.[48,49] This response is related to several signaling pathways such as autophagy, apoptosis, innate immunity, pro-inflammatory response, and MAP kinase pathways.[48] Further study has demonstrated that the virus can take over the ER by utilizing the stress sensor inositol requiring enzyme 1 (IRE1) which helps to regulate coronavirus-induced autophagy.[49] This ER response provides a potential pathway for immunomodulatory treatment.

Sigma-1 receptor (S1R) is an ER chaperone protein that regulates cytokine production through interaction with IRE1.[4] S1R modulation has demonstrated significant changes to coronavirus replication, and atypical antipsychotics with S1R activity have displayed protective effects against clinical deterioration.[50] Fluvoxamine is a selective serotonin reuptake inhibitor that is a powerful S1R agonist.[51] Fluvoxamine has previously been shown to protect mice from septic shock and reduce the inflammatory response.[52] There is potential for fluvoxamine as an immunomodulatory treatment for SARS-Cov-2. Fluvoxamine in CACO2 cells infected with

SARS-Cov-2 had a reduction in production of a subset of cytokines including IL-6, IL-8, CXCL1, and CXCL10.[53] A randomized controlled clinical trial of 152 patients showed that patients who received fluvoxamine were less likely to experience clinical deterioration, or serious adverse events due to SARS-Cov-2 when compared to placebo (0% vs. 8%).[4] A follow up real world observational cohort had similar findings of 0% (0/65) hospitalization with fluvoxamine vs. 12% (6/48) with observation.[54]



Ivermectin

Ivermectin has also shown anti-inflammatory effects that would reduce the harmful cytokine cascade noted in severe Covid-19 disease.[55] A recent trial assessing a multi-therapy including 12mg one-time dose of ivermectin found a 75% reduction in hospitalizations.[56] Another small double-blinded RCT showed significant increased chance of viral clearance after a 5-day course of ivermectin.[57] Another March 2021 RCT reported no effect on diminishing symptoms, but was under-powered for assessing reductions in hospitalization.[58] An RCT with ivermectin must be done in the US, as endemic strongyloidiasis in other countries may confound results.

Importance of factorial design approach:

It is important to study all 3 of these medications in a factorial design because they all fit into the same implementation category: all are existing, FDA-approved, generic, inexpensive, currently available world-wide, and have long records of excellent safety. They each hold few medication or co-morbidity related contraindications, and none of them require any follow-up for short-term use.

A factorial design approach is important for minimizing the percentage of patients who receive placebo in this urgent public health emergency. A factorial design allows us to efficiently compare the drugs directly to each other, as well as combination arms, while maintaining a placebo control. While EUA's and prospective cohorts have become common in the body of

literature about Covid-19, we feel that randomized placebo control is necessary for best understanding medication effect.

3.0 Study Endpoints

3.1 Primary Endpoint:

1) Clinical progression, defined as: Emergency department visit for any COVID-19 related symptom (including hospitalization or death) or decrease in O2 saturation (≤93%*[59] on room air, or need for supplemental oxygen to maintain an O2 saturation >93%) by 14 days.

COVID-19-related symptoms as defined by the CDC, or attributed to COVID by treating team. *https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Currently those symptoms include: Fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or running nose, nausea or vomiting, or diarrhea.

Secondary Endpoints:

- Clinical deterioration on a Likert-type scale: (0) No symptoms (1) moderate severity of illness as defined by O2 saturation ≤93% but no supplemental oxygen requirement; (2) O2 saturation >93% plus supplemental oxygen requirement; (3) ED visit for any COVID symptoms (4) hospitalization for any COVID symptom; (5) the above, plus ventilator support requirement; (6) the above, plus ventilator support for at least 3 days; (7) death;[4,60] and by number of days requiring supplemental oxygen; hospitalization; ventilator support), by Day 28. Hospitalized patients may be followed for maximal outcome.
- Time to meaningful recovery[61] (symptoms or severity improved by one category and sustained for at least 36 hours)
- Maximum symptom severity experienced by Days 14, 28 (Appendix B)
- Incidence of all-cause study medicine discontinuation (Day 14).
- Portion of participants with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
- a. PASC assessment monthly after enrollment for 6 months to 12 months with the "Questionnaire to characterize long COVID." (Appendix G).[62]
-

3.2 Laboratory Endpoints:

The first approximately 62 patients who are enrolled will be analyzed as a sub-study of continuous lab outcomes[63] comparing those on metformin versus placebo: C-reactive protein (CRP) level; albumin level; viral load; as well as microbiome changes (stool sample is optional for participants), from baseline to days 5 and 10.[64-66] (See Section 13 for more information)

*Patients will be asked to take a second reading if they have a reading ≤93% and to hold a hand-warmer for 5 minutes first to obtain good blood flow; to take the reading while sitting up; and advised to place the oximeter on the 4th finger (where skin is thinner).

4.0 Investigational Products

4.1 Description:

Metformin: a biguanide, administered in its immediate release (IR) formation, 1,500mg by mouth (typical dose for clinical use is 2,000mg per day). Patients will be instructed to take 500mg once on Day 1, ideally in the PM; 500mg in the AM and PM of Days 2-5; and 500mg in the AM and 1,000mg in the PM of Days 6-14.

Fluvoxamine: an antidepressant, administered in twice daily dosing, 50mg twice per day for 14 days (typical dose for clinical use is 100mg to 300mg per day).

Ivermectin: is an antiparasitic medication administered typically in ranges of 200-800mcg/kg/day.[67] In order to stay within this dose range, the following doses will be given in the following weight categories: 74 kg - 88 kg = 35 mg; 88kg – 106kg = 42mg; 106-124kg = 49mg; >124kg = 56mg. See details in Section 4.2. Treatment will be given for 3 days, and the remaining 11 days will be placebo tablets that exactly match the ivermectin in order to protect the blind.

4.2 Rational for formulation and dose:

Metformin: Given the current recall of Metformin Extended Release, ER, (see section on FDA recall below), availability of ER is limited. Additionally, it is possible that additional lots of ER will be recalled, further complicating supply issues and exposure to the recalled substance to patients. The side effect profile of immediate and extended release is similar, and we are limiting the dose at 1,500mg daily to balance the need to achieve a consistent dose and an effective dose without causing side effects, as the risk of side effects increase at a dose of 2,000mg daily.[68]

Fluvoxamine: A dose of 100mg TID was recently used in a small randomized trial,[4] and 50mg BID were recently used in a prospective cohort study.[69] The higher dose elicited side effects in approximately 10% of participants.[4] A separate ongoing phase III trial is now testing 100mg BID. We feel it is important to test a lower 50mg BID dose as the risks of side effects is lower and the public may be more willing to take an antidepressant medication if it is low dose. Additionally, the risk of serotonin syndrome and other drug interactions that may occur with fluvoxamine is lower with a lower dose, and thus persons currently on a serotonin reuptake inhibitor (SSRI) would not have to stop or alter their current therapy.

Ivermectin: we are using the standard release formulation (and only formulation) of ivermectin tablets. Given our lower BMI limit of 25kg/m^2, we do not anticipate enrolling many individuals weighing < 74kg. If someone weighs < 74kg or >124kg enrolls, the RC will contact the lead pharmacy for guidance on individual dispensing (regardless of treatment allocation, as the RC will be blinded to this), to keep the dose within approximately 390-470mcg/kg/day for the majority of patients, 350mcg/kg/day-480mcg/kg/day for all patients.

- We anticipate that most individuals enrolled will weigh between 68-104kg.
    - 35mg/day: is 390-470 mcg/kg/day for body masses of 74 to <88kg

- 42mg/day: is 390-470 mcg/kg/day for body masses of 88 to <106kg.
- 49mg/day: is 390-470 mcg/kg/day for body masses of 106 to <124kg
- 56mg/day: is 390-470mcg/kg/day for body masses of >=124kg

Acquisition:

A sufficient quantity of the FDA-approved formulation of metformin IR, ivermectin, and fluvoxamine IR for the study has been acquired by the MHealth Fairview IDS pharmacy.

4.3 Storage and Stability:

Store at room temperature up to 30ºC. Dispense in a tight, light-resistant container.

4.4 Pharmacokinetics:

Metformin: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Fluvoxamine: Onset of action: Anxiety disorders (obsessive-compulsive, panic, and posttraumatic stress disorder): Initial effects may be observed within 2 weeks of treatment, with continued improvements through 4 to 6 weeks (Issari 2016; Varigonda 2016; WFSBP [Bandelow 2012]); some experts suggest up to 12 weeks of treatment may be necessary for response, particularly in patients with obsessive-compulsive disorder and posttraumatic stress disorder (BAP [Baldwin 2014]; Katzman 2014; WFSBP [Bandelow 2012]). Depression: Initial effects may be observed within 1-2 weeks of treatment, with continued improvements through 4- 6 weeks (Papakostas 2006; Posternak 2005; Szegedi 2009; Taylor 2006). Distribution: Vd: ~25 L/kg
Protein binding: ~80%, primarily to albumin
Metabolism: Extensively hepatic via oxidative demethylation and deamination
Bioavailability: Immediate release: 53%; Extended release: 84%; not affected by food.
Half-life elimination: ~14 to 16 hours; ~17 to 26 hours in the elderly
Time to peak, plasma: 3 to 8 hours
Excretion: Urine (~85% as metabolites; ~2% as unchanged drug)

Ivermectin: Absorption: Well absorbed in the fasting state (Baraka 1996; Edwards 1988; Okonkwo 1993); may be increased with a high-fat meal (Duthaler 2020; Guzzo 2002; Miyajima 2013).
Distribution: V_d: 3.1 to 3.5 L/kg in healthy volunteers; mean 9.9 L/kg (range: 6.9 to 15.3 L/kg) in patients with onchocerciasis; high concentration in the liver and adipose tissue; does not readily cross the blood-brain barrier (Gonzalez Canga 2008; Okonkwo 1993).
Protein binding: ~93% primarily to albumin (Gonzalez Canga 2008)
Metabolism: Hepatic via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor)
Half-life elimination: 18 hours
Time to peak, serum: ~4 hours
Excretion: Feces; urine (<1%)

4.5 Dose Modification:

Participants will be advised to take ivermectin and its matching placebo on an empty stomach with water. Ivermectin and its matching placebo are provided in asmall blister-packed square.

Participants will be advised to take all other medications (i.e., metformin and/or fluvoxamine and their matching placebos) with a small amount of food (not on an empty stomach).

With mild side effects, participants will be reminded to take the tablets at the end of a meal, as opposed to the beginning of or "with" a meal. They will also be advised to stay upright for about an hour after consuming the study tablet.

With mild-moderate side effects, if the patients find them tolerable, patients will be advised the above, and that side effects should decrease after about 5 days of the medication. With moderate or moderate-substantial side effects that the patient finds intolerable, participants will be advised that they can break tablets in half if they feel they are having a non-tolerable medication side effect. Each type of active drug and placebo pill in this study can be broken in half. Dose modification will be recorded in the study database.

In the event of substantial side effects, participants may discontinue the study medication and stay in the study to complete follow up. This treatment discontinuation (whether in the placebo or any active treatment group), will not be considered study withdrawal.

4.6 Placebo:

The placebo will be tablet of microcrystalline cellulose, made to exactly mimic metformin or fluvoxamine or ivermectin.

4.7 Study Drug Handling:

Fairview IDS, part of M Health Fairview, will oversee the study and provision of bulk and pre-packaged study drug (including placebo) to participating sites. Participants will be given a study number coded by site (e.g. 01-001, 02-001, etc.). The pharmacy team involved will be unblinded to patient randomization. All other members of the clinical care team and the participants will be blinded to treatment allocation. The research team statisticians will remain blinded (additional information in Section 13, Statistical Considerations).

The IDS pharmacy will oversee the pre-packaging of the study drug into 2-week AM/PM pill packs for patients to improve compliance with the study drug regimen, improve safety (so they take the right number of each type of medication pill), and facilitate delivery to patients on the day of their consent. The research staff or pharmacy will select study drug based on the randomization code that preserves blinding, place the patient's name and study ID in the drug accountability log and study database, and place it in the study box for that patient and arrange for the delivery.

Pill packs will be labeled with the study name and PI name, contact information about the study; and the names and doses of all potential study drugs.

4.7.1 Provision of study drug to patients:

Following randomization, study drug to participants in an expedited way (for example courier, overnight mail service).

4.8 Study Unblinding:

Each participating pharmacy team, or the central pharmacy, will hold the blind for their site. Each site will have 24-hour access to the blind. Each subject will be provided information as to whom to contact for unblinding information in the event of an emergency. There is one unblinded statistician with two unblinded supporting statisticians on the study team.

4.8.1 Multiple strategies will be developed to assure that study drug is stopped at the time of hospitalization (as metformin is typically stopped at hospitalization for safety reasons)

4.8.2 Multiple strategies will be developed to inform patients and their medical providers that they are in study involving metformin or fluvoxamine or ivermectin, and that it should be stopped prior to imaging studies with contrast.

4.8.3 Multiple strategies will be developed to inform patients' medical providers that they are in a study involving metformin or fluvoxamine or ivermectin, and thus any potential interacting medications, or metformin itself, should not be started while the patient is in the study. The patient may withdraw consent at any time.

4.9 Biosafety:

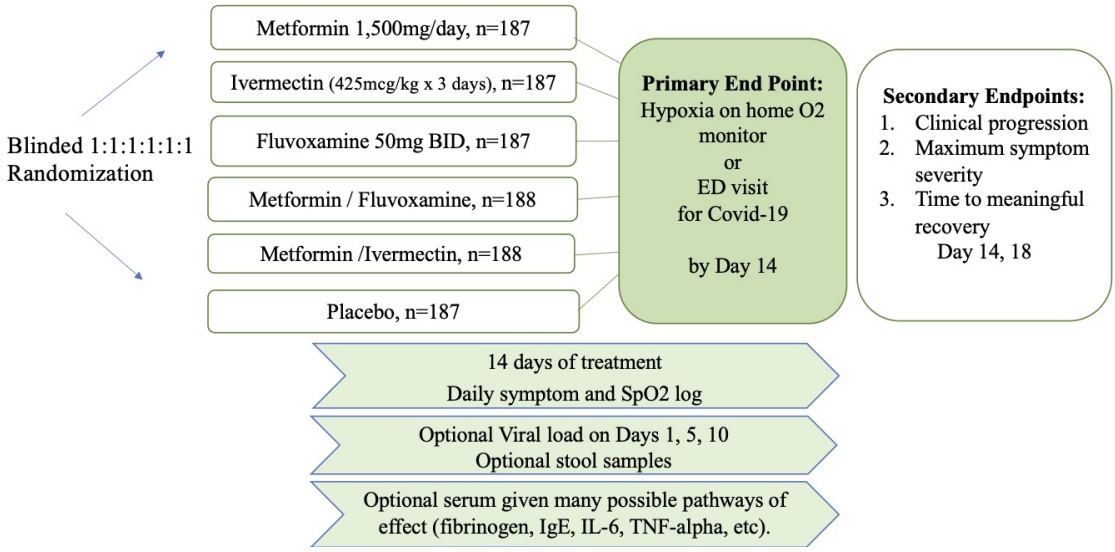
Patient samples will be carried in an expedited way (i.e. courier or mail services) in packaging that is approved for Biologic Substances Category B, UN 3373, per CDC guidelines for shipping SARS-CoV-2 samples: https://www.cdc.gov/coronavirus/2019-ncov/lab/lab-biosafety-guidelines.html#specimen

5.0 Study Procedures

5.1 Study Design:

Double-blinded, factorial, placebo-controlled randomized trial comparing metformin vs fluvoxamine vs ivermectin vs metformin + fluvoxamine vs metformin +ivermectin vs placebo for outpatient treatment of COVID-19 disease. This is an outpatient study. Study drug will be stopped at the time of hospitalization for any reason.

Overview of Study*:



*Updated sample size: 225 per arm, 1,350 total.

5.2 Recruitment

Advertising may be done by approaching patients who are scheduled to come for PCR testing, prior to or after their SARS-CoV-2 screening test, and before or after they may have the results. Advertising to patients before their SARS-CoV-2 test result is back allows the patients to consider the study and read about metformin and discuss with family. Receiving a positive SARS-CoV-2 test result will be overwhelming and make it challenging for patients to fully consider whether or not they want to participate. Being informed of the study before results are known will facilitate enrolling soon after their result is known so that study medication can be started early in the course of disease or soon after exposure.

Clinical teams may refer patients to the study in person or over the phone, including transferring patients to the study phone line if they are willing to be transferred. RC's may reach out to close contacts of persons with positive SARS-CoV-2 infection, and/or respond to patient emails, phone calls, or inquiries on the study website. The study teams may receive lists of persons who reach out to community patient advocacy groups looking for trials to enroll into. The central and participating site study teams may receive names and phone numbers of persons with a positive SARS-CoV-2 result from other facilities conducting testing. This information will only be in a secure database (Redcap or Box).

Patients may be given a brochure or electronic message with study information for contacting the study team if interested in this clinical trial. RC's may also pro-actively reach out to patients who are scheduled for SARS-CoV-2 testing or recently underwent SARS-CoV-2 testing either before or after they receive test results, as not all patients may receive or read an electronic message or brochure.

Patients can also self-refer based on seeing advertisements (such as through all forms of social media, newspaper, local posters, and email referrals).

Patients receiving test results by phone from the clinical care team may be alerted they may qualify for a research study and that study team members may contact the patient about eligibility.

Every attempt will be made to make sure the clinical team is informing patients of their SARS-CoV-2 testing results rather than the research team.

At times recruitment and enrollment efforts may be focused on priority populations within the eligibility criteria.

5.3 Screening:

- Based on patient feedback, to reduce participant burden because SARS-CoV-2 symptoms may be present, we will offer the opportunity for patients to self-screen online to avoid burden and barriers to participating
    - This will be performed via a web-based form. Eligibility criteria and medical history will be by self-report entries into the secure web-based form.
    - After self-screening online, patients may elect to self-consent online, or have a consent discussion with an RC (section 5.4).
- For patients who do not want to screen or consent via web-based form, screening and consent may be done over the phone with RC with eligibility criteria and history entered into the web-based form by the RC.
- Patients will be asked to submit proof of their positive SARS-CoV-2 result via secure means, but the receipt of the result may occur after enrollment.

5.3.1 GFR

GFR will be collected on persons > age 75 years or persons of any age who select or respond that they have chronic kidney disease, heart failure, or liver disease if a GFR is not available within 2 weeks in the EHR. It may be collected from patients by either self-collection kits sent to patients' homes with return arranged by the study team; or by local in-person collection.

Participants will receive the study drug at the same time as the GFR testing kit in the mail (or GFR drawn in person), as well as a return envelope for the study drug. They will start the study drug before their GFR result is returned. If the GFR result returns and is < 45ml/min, they will be asked to stop taking the study drug and return the remainder of the study drug. This will count as a screen failure.

We are taking this approach for 3 reasons: a) this is consistent with clinical practice in which metformin us often started while a GFR result is pending, because the use of metformin for two weeks at a dose of 1,500mg does not significantly increase risk of lactic acidosis in someone who has no known history of severe heart, liver or kidney injury, including in persons with COVID-19;[70] b) to start the study drug early in the course of the disease, as in real life an outpatient post-exposure prophylactic or treatment therapy would be offered at the time of SARS-CoV-2 exposure or positive infection, c) maintain a virtual study design so as to not create unnecessary exposure and use of PPE by having labs drawn in person. Metformin is FDA approved down to a GFR > 30ml/min, though sometimes used down to a GFR of 15.[71]

For any in-person contact, all measures will be taken to mitigate risk of SARS-CoV-2 exposure to the phlebotomy or study team members, and to the participant.

Optional serum samples

Serum samples (approximately 20-30cc) will be collected on patients who are willing to provide these samples, via mobile phlebotomy to their home, to better understand treatment response and mechanism. A random sample of 95% of these samples will be analyzed. Labs will be processed at local eligible labs, or at the University of Minnesota Advanced Research and Diagnostic Laboratory, which is a CLIA-certified, CAP-accredited clinical testing laboratory that is certified to receive, process and test samples from COVID-19 patients. Any antibody samples will be conducted by FDA-approved assays or academic institutions that have validated their assays.

5.4 Informed Consent

Consent will be obtained (via self-consent (below), or a traditional consent conversation) before beginning any study procedures. The entire consent document will be reviewed, including all study procedures and expectations, risks, benefits, and what volunteering means. Participants will be asked questions to gauge their level of understanding.

Potential participants will be given time to read the consent and ask questions. If needed, a participant may take additional time to review the consent or discuss participating in the study with family/friends. The consent conversation will be done remotely, using a phone or secure HIPAA compliant video/web conferencing or in-person.

Based on patient feedback, we will also offer the opportunity to self-consent online, waiving the consent conversation. This would mean that after potential participants answer eligibility questions with the RC or online (section 5.3 above), they could access the online consent module.

- Patients will be able to read the consent form online and asked to answer comprehension questions about the consent. Participants will review short sections and need to click in order to move to the next section to increase engagement and comprehension of the study during the self-consent process.
- If their responses to the comprehension questions indicate that they are well-informed about the study, they would be able to sign the consent form online.
- If their responses indicate that they lack understanding, the RC may call them for a traditional consent conversation and assessment of comprehension.

The consent document will be presented to the participant as an electronic document (eConsent) through the University of Minnesota's instance of REDCap. The REDCap eConsent document will contain the full consent text and is compliant with FDA 21 CFR Part 11 for the electronic capture of signatures. Participants will be sent a link via email or text to the REDCap survey which will contain the full consent text. After signing the consent, participants will receive an electronic copy of the signed document or a paper copy if in-person. Consent may also be done in person via hard-copy print out of the consent form if patients are in clinic for other reasons.

5.4.1 Non-English Speaking Participants:

Non-English speaking patients will not be specifically targeted for enrollment, but any non-English speaking participants will be consented using the short form consent process.

Before consenting, the study team will ensure that a suitable interpreter will be available during the consent process and throughout the study. For any non-English speakers who are enrolled using the short form consent process, a certified translation will then be obtained for the long form consent form in the participant's preferred language. After the IRB approves this document, the participant will be re-consented using the translated form.

Enrollment:

Eligible patients will be randomized to metformin IR or fluvoxamine or fluvoxamine + metformin or ivermectin or ivermectin + metformin or placebo and will receive the study drug by courier or mail service with every effort made to deliver the drug same-day or via overnight delivery.

Medication regimen:

Metformin or Placebo: Participants will be advised to take 1 pill by mouth on Day 1, ideally in the evening; and 1 pill by mouth approximately every 12 hours starting Day 2; and 1 pill by mouth in the AM and 2 in the PM day 6 and onwards, and to take pill at the end of a balanced meal and to stay upright for at least an hour after taking it.

Fluvoxamine or Placebo: Participants will be advised to take 1 pill by mouth on Day 1, ideally in the evening, and 1 pill by mouth approximately every 12 hours for Days 2 – 14.

Ivermectin: Participants will be advised to take any blister-packed tablets on an empty stomach.

The following data points may also be collected, if available, by self-report or EHR review:

- Name; Date of birth; Medical record number (if applicable); Phone number; Email
- Contact information for family members to assist with follow-up if needed
- Age; biologic sex; Race; Ethnicity; Insurance status (if available); Zip code
- Location of initial sample collection for diagnosis, Location of assessment
- Date and time of initial sample collection for diagnosis
- Date and time of positive test result for COVID-19
- Date of first symptoms
- Date of first fever, if applicable (temperature >100.5°F)
- Patient-reported comorbidities [for example: hypertension (requiring or not requiring medication), diabetes mellitus (insulin or non-insulin dependent), coronary artery disease, myocardial infarction, congestive heart failure (with preserved or reduced ejection fraction, if known), pacemaker or AICD, asthma (with or without emergency department evaluation and / or hospital admission in the past year), chronic obstructive pulmonary disease, chronic bronchitis, chronic steroid use, history of transplant (with type), arrhythmias including atrial fibrillation, dialysis, angina, pulmonary hypertension and obstructive sleep apnea, renal disease, liver disease, tobacco and alcohol use history, recent or current pregnancy or breastfeeding history, and height and weight at study start and completion.]
- Self-reported home medications [for example: antihypertensives, insulin, non-insulin diabetes medications, corticosteroids (inhaled, systemic), other immunosuppressants hydroxychloroquine, other COVID-directed treatments or vaccines] or home oxygen use

- Use of outpatient COVID-directed treatments (such as Tylenol, ibuprofen, azithromycin, or others); whether or not they received the 2020/21influenza or COVID-19 vaccines.
- Medication adherence, known exposures, symptoms and side effects

The following data points may also be collected, if available, by self-report or EHR review:

- Vital signs at presentation to ER or urgent care (if recorded)
- Clinical laboratory results at presentation (if recorded)
- Hospital admission (with date, if applicable)
- Date of death (if applicable)
- Study withdrawal, with date and time (if applicable)

5.4.2 Retention:

All study staff members will be informed of the importance of retention and steps to prevent missing data. RC's will be advised to contact participants a second time per patient contact point if they are not able to reach the participant after the 1st contact. RC's may call, video, text, or email with patients on Day 2 to assess side effects or questions. If patients experience side effects, the RC's may remind patients of approaches to minimize side effects (See Section 4.3), and to advise the patients that side effects usually subside after about 5 days.

5.4.3 Lab Collection:

Labs will be considered optional if patients want to participate but not collect the nasal swab and/or stool. For interested and willing patients, labs will be done on approximately Day 1, 5, and 10.

The SARS-CoV-2 PCR may be assessed via self-collect anterior nasal swab, which may be done over phone or video with the RC if the patient prefers this aid. Detailed instructions for the patient are in Appendix B, the patient manual.*

The GFR blood tests may be collected by the clinic, mobile phlebotomy, or finger-prick, with the option of it being done while on secure video or phone with the RC if the patient prefers this aid. Blood will be collected in a microtainer tube and placed in approved shipping materials that will then be returned to the lab via courier or mail.

Stool sample collection is optional and would be done with a self-collect microbiome kit. Patients will be given detailed lab collection procedures for each test.

Missing biospecimens will not constitute protocol deviations.

5.4.4 Seeking Medical Care:

Patients will be advised to seek medical care, as they would if they were not in the study, including other treatments of Covid-19. Participants will be advised that the distribution of home oxygen monitors is not meant to prevent them from seeking medical care, and that they should seek medical care as they would whether they were in the study or not.

5.5 Follow-up Procedures:

Data on clinical progression may be collected on any consented patient by EHR review, from contact if patient not available, by patient self-report (phone, survey, email, text), or by vital records search.

RC's may contact patients on Day 2 to assess side effects or questions. If patients experience side effects that they find distressing, the RC's will discuss approaches to minimize side effects (See Section 4.6 Dose Modification), and to advise the patients that side effects usually subside after about 5 days.

Participants will be asked to track symptoms (including temperature and oxygen saturation), and medication adherence daily. Patients will receive a thermometer and oxygen saturation monitor with their study drug (details below). Study personnel will attempt to contact with patients about every 2 to 3 days during the 14-day intervention window to review study drug adherence, and review symptoms for possible adverse events.

Patients will be followed for 28 days for disease severity. Follow-up contact with patient or family and electronic medical record review will determine the primary and secondary efficacy endpoints.

A patient who has a visit to an emergency department for COVID-19 related symptoms, (determined by current CDC definition of COVID-19 related symptoms or treating team), or hypoxia (two measurements of O2 saturation ≤ 93% or supplemental oxygen required to maintain saturation >93%) will have achieved a positive result for the primary outcome.

Patients who experience a primary outcome before enrollment (i.e. ED visit at which they received their +SARS-CoV-2 result) will be followed for occurrence of a primary or secondary outcome after T0 (Day 1 in the study).

- Patients who are hospitalized will stop the study drugs.
- Secondary outcomes will be assessed at 14 and 28 days, including in patients who drop out of doing the study tasks. EHR search of outcomes will be assessed of all patients who enroll.
- Patients in the treatment arm who visit an urgent care or emergency department and are sent home without being admitted should continue the study drug through day 14, unless otherwise directed by the treating physician in the emergency department or urgent care.
- Long-Covid symptoms will be assessed at approximately 1-month intervals after the completion of the 14-day study treatment period.

<u>Oxygen Saturation:</u>

For the daily oxygen saturation recording, participants will be asked to measure their oxygen level ideally in the afternoon or evening. They may take a reading at any time, especially if they feel short of breath or are breathing faster than normal. If they have an oxygen saturation ≤ 93% on room air on 2 readings or more, they will be advised to call their doctor's office (or go to the ED if they feel they need to). If a study participant develops a decrease in oxygen saturation to less than 90% on room air on >2 readings,

the research staff will direct them to seek emergency medical care at the nearest ED. Research staff may call 911 on behalf of the patient, or otherwise engage the patient's medical provider, if they feel the patient is not able to do this on their own.

Referral to medical care: If the research staff feels a patient is unwell, they will advise the patient to reach out to their doctor. Physician investigators may also evaluate the participant via phone/telehealth and direct them for further care if needed.

When a participant is directed to seek emergency medical care, they will be instructed to identify themselves to EMS or to the ED staff as having been diagnosed with COVID-19.

5.5.1 Survey Data Collection:

Participants will be given a hard-copy symptom log to capture COVID-19 related symptoms daily (Appendix B). Patients will be asked to record their medication adherence, their temperature, and their oxygen saturation with a home O2 monitor every day for the 14 days of participation.

The symptom log may also be available by Part-11 approved means (such as via text or app). For patients not using app, RC's will assess whether the symptom logs are being filed out daily at each contact point with patients. Adherence with taking the medication will be assessed via self-report daily in the log or software to record adherence.

Survey questions will be listed in a physical paper study log that is included in the study box that is sent to patients. Patients can fill out the survey on these paper logs and then send a picture of the logs to study staff (no identifying information on the pages of the logs); patients can also receive the survey questions via Part 11-certified electronic means; or patients can report the survey question answers to the RC over the phone if they prefer.

5.5.2 Timeline of Events:

Every attempt will be made for the contact points with patients to be done in the way that they prefer (i.e. text, phone, email, video):

Day 1 Contact: Verify receipt of study drug, participant starts study drug. If multiple participants live in the same household, they will be reminded to keep all of their study materials labeled with their own participant ID and separated from the other participants.

- Phone or video visit to walk through procedures for obtaining lab values if the patient desires.
- RC will arrange for the lab samples to be returned.
- Patient records symptoms (via symptom log adapted from FDA suggestions, Appendix B), RC does not need to collect over phone.

Day 2 Contact:

- Patient records side-effects (PROMIS diarrhea survey, Appendix C)
- Patient records symptom/adherence log (adapted from FDA suggestions, Appendix B)
- Assessment of clinical progression

- Query for medication-related side effects / AEs

Day 3/4: RC will follow-up results of GFR for patients for whom GFR was indicated. If the GFR is < 45ml/min, the RC will have the patient return the remaining study drug in one of the return envelopes provided and will arrange for this shipping.

Day 3, 4: Symptom/adherence log (adapted from FDA suggestions, Appendix B)

Day 5 Contact:
- Symptom/adherence log (adapted from FDA suggestions, Appendix B)
- Assist with return shipping of optional labs (viral load, stool)
- Assess clinical progression

Day 6-9: Symptom/adherence log (adapted from FDA suggestions, Appendix B)

Day 10 Contact:
- Symptom/adherence log (adapted from FDA suggestions, Appendix B)
- Assess clinical progression (Query for hospitalization or ER visit or SAEs)
- Assist with return shipping of optional labs (viral load stool)

Day 11-13: Symptom/adherence log (adapted from FDA suggestions, Appendix B)

Day 14 Contact:
- Symptom/adherence log (Appendix B)
- Assess clinical progression

Day 28 Contact:
- Symptom log (adapted from FDA suggestions, Appendix B)
- Assess clinical progression (Query for hospitalization or ER visit or SAEs that occurred between Day 14 and Day 28)
- Assess other medicines used during study period

A vital status search will be conducted on all randomized patients.

Days are +/- 3 days, for the first 14 days every attempt will be made to capture data +/- 1 day.

Patients will be advised to seek medical care for symptoms in the same way that they would if they were not in the study.

Participants will be reimbursed for their time via a trackable means (i.e. Clin card or Visa card), after completion of these study activities: enrollment; Day 1 labs; Day 5 labs; Day 10 labs; Day 14 log returned; and Day 28 follow-up.

Monthly Contact: Patients will be assessed approximately once/month for 9 months after the completion of their Day 28 contact to assess for ongoing symptoms suggestive of post-acute sequelae of COVID-19. Patients will receive reimbursement for each of these monthly follow-ups completed.

5.6 Study Duration:

14 days of treatment with follow-up, and a follow-up survey at 28 days then monthly for 9 months.

Schedule of Assessments:

Symptoms: Days 1- 14, 28.

Side effects: Day 2

AE's/SAE's: Days 2, 5, 10, 14, 28

Clinical Progression: Days 5, 10, 14, 28

PASC: Monthly after Day 28

5.7 Retention:

We will make every effort to keep participants engaged through the entirety of the study so as to minimize missing data (for example regular calls, texts, emails, assessment via vital records search, and contact with family members if needed). The principal investigators have recent experience working with patients on COVID-19 trials, and they will leverage this experience.

6.0 Study Population

6.1 Study Population:

Adults age 30-85 years with no prior history of SARS-CoV-2 infection and with BMI in overweight or obesity category. We will not exclude patients who have diabetes, but we will exclude patients on insulin or a sulfonylurea. Symptoms are not a requirement to enroll in the because of their subjective nature and because of wanting to start patients on study drug early in the disease course.

6.2 Inclusion and Exclusion Criteria:

Inclusion criteria	Exclusion criteria
- Positive laboratory test for active SARS-CoV-2 viral infection based on local laboratory standard (i.e. +PCR) within 3 days of randomization. - no known history of confirmed SARS-CoV-2 infection - Age >=30 years and < 85 years - BMI >= 25kg/m^2 by self-report height/weight or >= 23kg/m^2 in patients who self-identify in Asian or Latinx background.[72-74] - Has an address and electronic device for communication - GFR>45ml/min within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure.	- Hospitalized, for COVID-19 or other reasons. - Symptom onset greater than 7 days before randomization (symptoms not required for inclusion). - immune compromised state (solid organ transplant, bone marrow transplant, AIDS, on chronic high dose steroids) - Hepatic impairment (Child-Pugh B and C) or that in the opinion of the investigator, would affect safety - Inability to obtain informed consent - Enrollment in another blinded RCT for COVID-19 - Already received an effective (FDA approved/EUA*) therapy for COVID-19 (currently monoclonal antibody treatment) - Alcohol use disorder

	- Other unstable medical condition or combination of home medications that in the view of the PI make it unsafe for the individual to participate - History of severe kidney disease i.e.: • Stage 4 or 5 CKD, or Estimated Glomerular Filtration Rate (eGFR) of < 45ml/min/1.73 m^2 • Other kidney disease that in the opinion of the investigator would affect clearance - Unstable heart failure (Stage 3 or 4 heart failure) - Current use of metformin, fluvoxamine, or ivermectin - Bipolar disease: individuals who report they have bipolar disorder or are taking medication for bipolar disorder (lithium, valproate, high-dose antipsychotic), unless the investigator concludes that the risk for mania is unlikely (i.e. it is doubtful that the patient actually has bipolar disorder). - allergic reaction to metformin in the past - allergic reaction to fluvoxamine in the past - allergic reaction to ivermectin in the past • *current loa loa or onchocerciasis infection* • *typhoid, BCG, or cholera vaccination within the 14-days or 3 days after* <u>Medication Exclusions:</u>[75] - cimetidine, hydroxychloroquine, insulin, sulfonylurea, dolutegravir, patiromer, ranolazine, tafenoquine. - rasagiline, selegiline, or monoamine oxidase inhibitors, linezolid, methadone - Duloxetine, methylene blue - Tizanidine, ramelteon, sodium picosulfate - Alosetron, agomelatine, bromopride, dapoxetine, tamsimelteon, thioridazine, urokinase, pimozide The following medications may not need to be excluded when dose for that individual is considered alongside the low dose of fluvoxamine being used and other medications being used. The PI or site PI may review and decide if the patient should be excluded from the fluvoxamine arms: 1. Taking SSRIs, SNRIs, or tricyclic antidepressants, unless these are at a low dose such that a study investigator concludes that a clinically significant interaction with fluvoxamine (ie either serotonin syndrome or TCA overdose) is unlikely (examples: participant takes escitalopram but only at 10mg daily; that dose plus 100mg fluvoxamine would be insufficient to cause serotonin syndrome; or, participant takes amitriptyline but only at 25mg

	nightly; even if fluvoxamine inhibits its metabolism, it would be an insufficient dose to cause QTc prolongation or problematic side effects). *Risk Class C, monitor therapy.* 2. Individuals who take alprazolam or diazepam and are unwilling to cut the medication by 20% (rationale: fluvoxamine modestly inhibits the metabolism of these drugs). *Risk Class C, monitor therapy* 3. Participants taking theophylline, clozapine, or olanzapine (drugs with a narrow therapeutic index that are primarily metabolized by CYP 1A2, which is inhibited by fluvoxamine) will be reviewed with a study investigator and excluded unless the investigator concludes that the risk to the participant is low (this would be unlikely; example: participant takes clozapine only as needed and is willing to avoid it for the 14 days of the study). 4. Patients will be advised that there is a small risk that the following substances will be affected by fluvoxamine, but that significant effects are not likely at the low dose being used: 1. caffeine, nicotine, melatonin. *Risk Class C, monitor therapy* *5.* Taking warfarin-also known as Coumadin, NSAIDs, and Aspirin (rationale: increased risk of bleeding), phenytoin (rationale: fluvoxamine inhibits its metabolism), clopidogrel (rationale: fluvoxamine inhibits its metabolism from pro-drug to active drug which raises risk of cardiovascular events), and St John's wort (rationale: fluvoxamine + St John's wort are considered contraindicated because of the risk of serotonin syndrome) Risk C, monitor therapy.

*Additional COVID-19 treatments to exclude will be decided by a panel of at least 3 Co-Investigators on this study. The additional treatments to exclude will be documented and submitted to the IRB but may be implemented before formal IRB approval is complete. We take this approach because of the rapidly changing treatment landscape of COVID-19.

6.3 Vulnerable Populations:

By nature of the disease and the fact COVID-19 is a rapidly evolving pandemic, with uncertain clinical course but potentially significant morbidity and mortality, <u>all</u> participants enrolled in this study are considered to be vulnerable. Some participants have additional characteristics that add to this vulnerability. Our criteria for inclusion and exclusion of each of these groups is summarized below, followed by our rationale and additional safeguards built into our study design. <u>Our group has significant experience enrolling vulnerable patients in emergency care trials</u>, and experience with a diverse population of potential participants in high stress situations.

COVID-19 is disproportionately impacting low-income communities and persons of color, and these reasons are multifactorial. It is important to include individuals of diverse backgrounds in

this research. It is also important to not present this research in a coercive way to individuals with low income and who come from traditionally marginalized backgrounds. We have chosen participating sites throughout the US based on sampling diverse populations throughout the US (i.e. areas serving primarily Black and Latinx populations), areas where there are high incident rates, and areas with experienced PI's.

6.3.1 Additional Safeguards:

- *Non-English speakers:* Excluding this group would compromise the principle of justice in clinical research. For groups likely to be enrolled given our known demographics (for example, Spanish-speaking and Somali-speaking), we will translate informed consent forms (ICF) and use professional interpreters during both the consent and follow-up periods. These interpreters are available to our group during daytime hours by telephone. *We will request the use of the Short Form Consent for non-English speaking participants, and adhere to the regulations surrounding its use. When the translated ICFs become available, they will be used for non-English speakers.* We will make every effort to have Spanish-speaking research coordinators on our team and access to interpreter services.
- *Employees or students of the researcher:* This group will be excluded.
- *Undervalued or disenfranchised social group:* We will assure confidentiality, that they have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions.
- *Active members of the military (service members), DoD personnel (including civilian employees):* The status of participants of this group is not asked during the study nor known by study staff, and therefore vulnerability is not increased for anyone in this group.
- *Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare:* We will assure that information from participants in this study will be treated with the strictest confidentiality, that participants have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions. When needed, every effort at making accommodations will be made for those who do not have a home address, such as medication pick-up space in a local shelter or emergency department. If the potential participant needs a phone in order to comply with study needs, one will be provided for the duration of the individual's enrollment.
- *Individual or group with a serious health condition for which there are no satisfactory standard treatments:* We will assure confidentiality, that they have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions. We will also employ the teach-back method to ensure participants understand risks and demands of study participation.
- *Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior):* The status of participants from these groups is not asked during the study nor known by study staff, and that vulnerability is not increased for anyone in this group.

6.4 Number of Participants

Enrollment will occur remotely via the previously described methods for interested participants presenting to one of the PCR-testing sites or via self-referral to the study. Patients in assisted

living facilities do qualify for this study. The total number at each site will be affected by local incidence rates at the time of enrollment. We anticipate that at least 100 participants will be enrolled at each participating institution.

7.0 Sharing of Results with Participants

7.1 Sharing of results:

Data collected within this study will be obtained from the participants themselves or will be obtained from the electronic medical record and thus are already available to the patient and treatment team. Any testing of biospecimens will occur at a later time point and do not have specific clinical relevance. Research results will be shared with the participant and/or the participant's primary care provider when determined by the research clinician to be clinically relevant.

7.2 Sharing of genetic testing

Not applicable. No genetic testing will be conducted

8.0 Withdrawal of Participants

8.1 Withdrawal Circumstances:

Participants may withdraw from the study at any time for any reason. Participants may be withdrawn from the study without their consent if at any point they develop an exclusion criteria that makes it unsafe for them to continue in the study. All data from patients withdrawn from the study will be analyzed up until time of withdraw. Clinical progression after withdrawal may be assessed via EHR or vital status review or by reaching out to patients or their contacts.

8.2 Withdrawal Procedures:

If patients choose to withdraw, study procedures including intervention and follow-ups will stop. Given the remote nature of this study, written notification is not required. If the patient chooses to withdraw, the study team will ask if the patient is willing to allow continued electronic medical record evaluation for the determination of study endpoints (partial withdrawal). We will also ask if the patient wishes to withdraw consent for the use of future biologic specimens. If the patient declines to participate in any component of research, no further study data will be collected, biologic samples will be destroyed, but existing study data may be used. Each of these circumstances will be documented and stored as a study document.

8.3 Termination Procedures:

Upon trial termination, study outcomes will be followed until completion. Case report forms and collection templates will be maintained in paper format (when applicable) and electronically for 7 years in accordance with regulations. Collected data will be used for secondary analyses with approval of the principal investigators in a deidentified fashion. Data entry will be completed, checked for accuracy, and locked for analysis within 1 year of enrollment of the final patient.

9.0 Risks to Participants

Metformin: Metformin has been safely used since the 1920s, making it an appealing option for treatment in asymptomatic individuals.[76] The most common side effects are gastrointestinal (GI), and typically happen in fewer than 15% of patients; GI side effects are minimized when metformin is taken at the end of a meal (rather than at the beginning or "with" a meal), and often subside after 5 days of regular use.[68] The most common GI side effects are:

- nausea, vomiting, stomach pain;
- lose bowel movements
- diarrhea

We are not obtaining safety labs after starting the trial because we are not including patients on medications that increase risk for hypoglycemia (insulin and sulfonylureas), and the package insert recommends GFR monitoring only every 12 months, and monitoring B12 levels every 2-3 years in patients at risk for B12 deficiency, as participants will not be taking study drug for more than 14 days.

Fluvoxamine: Fluvoxamine has been safely used since the 1980s. The most common side effects are central nervous system and gastro-intestinal. About 10 to 30% of patients may experience headaches or insomnia, particularly at higher doses. About 10 to 40% or patients may experience nausea or diarrhea, particularly at higher doses. The dose used in this trial is lower than the dose typically used in clinical care with fluvoxamine.

Ivermectin: Ivermectin has been safely used since the 1980's. Use during infection with onchocerciasis is associated with more side effects, so persons with concomitant infection are excluded. In the absence of onchocerciasis, about 4% of persons will have tachycardia; 2% will have diarrhea/nausea; and 3% will have dizziness. About 2% to 3% of persons will also have laboratory changes (changes in CBC or transaminase levels).

See Metformin, Fluvoxamine, and Ivermectin Packet Inserts for additional drug information and risks.

9.1 Mitigation of Risk:

Metformin:

- Elevated levels of NDMA have not been found in metformin IR, immediate release. We will only use immediate release metformin, not extended release.
- In order to reduce the risk of lactic acidosis, we are excluding patients with advanced heart failure, liver failure, or renal failure, or known alcohol use disorder
- We are requiring a baseline GFR in persons > age 75, or with history of heart, liver, or renal failure, within 2 weeks before enrolling to ensure those high risk patients have a GFR > 45.

Fluvoxamine:

- We are using a low dose of fluvoxamine with only 1 dose on the first day to mitigate side effects from BID dosing on the first day.

- Ivermectin:
- While the range of acceptable and safe per kilo doses of ivermectin is large, we are using weight-based dosing.

All arms:

- We will use careful screening of exclusion criteria so that participants are excluded from arms that may include a contraindication or medication interaction.
- We are recommending that study drug be taken at the end of a small meal, and that patients abstain from alcohol use during the study period.
- We are creating an upper age limit in order to reduce the likelihood of a patient experiencing reduced GFR during the study period.
- Patients will be advised to let their providers know that they are in a research study that involves metformin, ivermectin, or fluvoxamine, and thus that they should discontinue the study medication at the time of hospitalization or before a CT scan with contrast.
- Every effort will be made to enter a Research Note into the electronic health record stating that the patient is in a double-blinded randomized trial of metformin, fluvoxamine, ivermectin, and placebo with the study number and contact information for participants who are enrolled from participating health systems.

9.2 Reproduction Risks:

While fluvoxamine and ivermectin may be used in pregnancy and have no known teratogenic effects, they have not been assessed in prospective randomized trials in pregnancy as often as metformin has. Thus, we will close the randomization arms that include ivermectin or fluvoxamine to pregnant women. We will have a separate group of blinded study packs for pregnant and lactating women, so that study staff will know that pregnant and breastfeeding participants are getting only either metformin or placebo, but will remain blinded to whether they are receiving metformin or placebo. Additionally, because pregnant and lactating women will be considered their own sub-study in this trial, and an important sub-study, we will enroll pregnant/lactating women down to age 18 years old. Thus, pregnant women may be analyzed as a separate substudy.

Metformin has not been found to have teratogenic effects and is commonly used in pregnancy, so we do not have a justification to exclude pregnant women.[77-80] Pregnant women will be advised to inform their care providers that they are in this study. As with all participants, study procedures may be done completely virtually. If a participant prefers in-person lab draws or other procedures, every possible effort will be made to follow current standards of protecting the subject and study staff against transmission of the virus.

10.0 Outcomes that are specific to pregnancy, https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm, will also be analyzed (they would all be captured as a hospitalization or ED visit, the primary outcomes for the main study). Potential Benefits of Treatment Arms

10.1 COVID-related potential benefits of Metformin:

10.1.1 Observational data show associations of reduced mortality from COVID-19 in patients using metformin.[2,81,82] There is un-published observational data showing decreased likelihood of being hospitalized for patients on home metformin. Metformin has been

associated with improved outcomes in other viruses (Influenza and Zika, another RNA virus).[42,45]

10.2 COVID-related potential benefits of Fluvoxamine:

10.2.1 Fluvoxamine has been shown in a phase 2 trial and prospective cohort, as well as in vitro-studies and computer modeling, to decrease severity of COVID-19 disease.[4,50]

10.3 Covid-related potential benefits of Fluvoxamine:

10.3.1 A recent trial assessing a multi-therapy including 12mg one-time dose of ivermectin found a 75% reduction in hospitalizations.[56] Another small double-blinded RCT showed significant increased chance of viral clearance after a 5-day course of ivermectin.[57]

10.4 Other possible benefits:

Metformin has been associated with reduced incidence of blood clots, improved outcomes in some cancer, improved cholesterol, and improved insulin resistance, in patients with and without diabetes.[7,9,10,83,84]

Metformin is commonly used as a chronic medication for type 2 diabetes, pre-diabetes, and often off-label use for weight management, poly-cystic ovarian syndrome, and preventing anti-psychotic related weight gain.[80]

Additionally, 34.5% of adults in the US have prediabetes,[85] and 90% of them have never been told about this diagnosis.[86] Metformin is indicated for many persons with prediabetes, however only about 1% of persons with prediabetes have been prescribed metformin.[87]

11.0 Data and Specimen Banking

11.1 Storage and Access:

Study data will be recorded and retained within a University of Minnesota REDCap database with study personnel being granted access to the database based on need as listed in the Delegation of Authority log.

The electronic consent (eConsent) forms will be maintained in a University of Minnesota REDCap database.

Biologic specimens intended for research beyond the study outcomes, provided by patients, may be processed by the University of Minnesota BSL2+ laboratory and frozen at -80 C. Samples will be deidentified and labeled only with a patient's study ID number.

Only authorized study team members will have access to data/specimens, expect as detailed in section 11.2.

11.2 Release/Sharing:

Data will be shared among members of the study team with appropriate access based on study role, training, and delegation of authority. Data will be made available to assigned study monitors, the data safety monitoring board, the appropriate University of Minnesota oversight

authorities, the Food and Drug Administration, and other state and federal regulatory authorities as required by state and federal law.

De-identified specimens and data may be shared for future research. Requests will be evaluated on a case-by-case basis. No data will be released without proof of IRB approval or determination. Agreements as required by local policies will be completed when necessary, including data use agreements and material transfer agreements.

12.0 Statistical Considerations

A detailed statistical analysis plan (SAP) will be included as an appendix and developed by the statisticians prior to analyzing unblinded data. The SAP may be amended as needed thereafter by the blinded statistician(s). All analyses will follow a modified intention to treat (mITT) approach, excluding participants who were screen failures or who did not ingest any study drug, unless specified otherwise.

12.1 Randomization:

Eligible and consenting participants who test positive will be enrolled and randomized evenly among the arms for which they are eligible, i.e. 1:1:1:1:1:1 for participants who are eligible for all 6 arms. Randomization will be stratified by study site from which their IP is dispensed. Stratum specific schedules will be preemptively generated using mass-weighted urn randomization with a total mass of $\alpha = 6$, which is a generalization of randomly permuted blocks that reduces predictability of future assignments.[88] Patients eligible for one study drug and ineligible for another, who are still interested in the trial, may be randomized amongst the study drug arm for which they are eligible. Randomization schedules will be generated for each possible drug eligibility pattern, and assignments will be drawn sequential from each stratum specific sequence therein. Statistical analyses will be study drug specific and consist of all participants who were eligible for and randomized into the relevant arms. Direct comparisons of study drugs and evaluation of drug-drug interactions will be conducted amongst participants who were eligible for both drugs in the comparison/interaction.

12.2 Blinding:

Study drug will be prepared by an unblinded study pharmacy team. Study personnel and participants will be blinded to participant assignments and outcomes data for the duration of the study, excepting lab data as detailed below and situations that require the blind to be broken for safety reasons. These instances will be recorded and reported to the PI and DSMB. An un-blinded analysis of the laboratory outcomes from the treatment cohort sub-study will be carried out by the unblinded statisticians and shared with the blinded investigators and potential sponsors of the trial.

12.3 Sample Size Assumptions:

The statistical design is for the comparison of metformin vs placebo, controlling for the effect of fluvoxamine and ivermectin.

Sample size estimates are based on a marginal test of metformin versus placebo comparison, controlling for fluvoxamine and ivermectin use, and selected to provide at least 80% power with

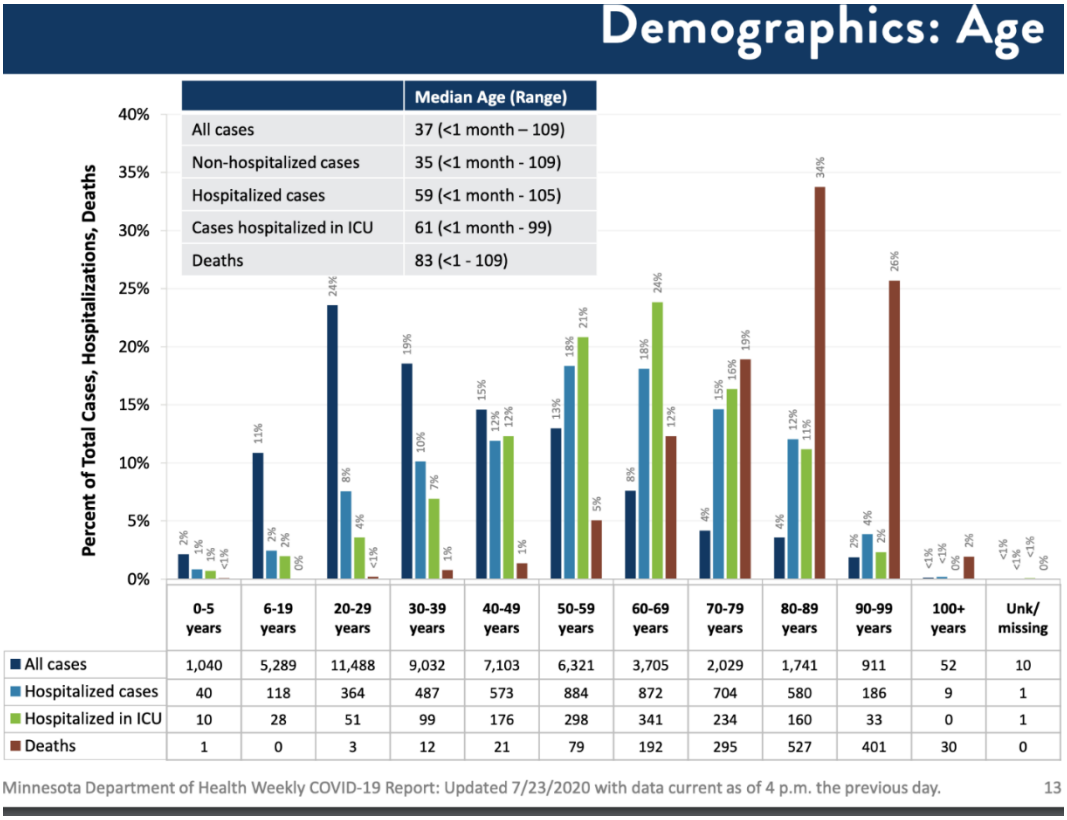
5% two-sided type I error rate for the target effect indicated by the event rates in the above figure and described in detail in subsection 12.3.1. The sample size estimates are also inflated by 11% and rounded to account for interim analysis plan (see subsection 13.4) and study withdrawals.

Factorial design maximizes the use of placebo

Each patient gets 2 types of pills	**Metformin (n=563)**	**Placebo (n=187)**	
Fluvoxamine (n = 375)	Metformin / Fluvoxamine n =188 6% event rate if both effective	Fluvoxamine / placebo n=187 11% event rate	
Ivermectin (n=375)	Metformin/Ivermectin n = 188 6% event rate if both effective	Ivermectin/Placebo n = 187 11% event rate	
	Metformin / placebo n = 187 11% event rate	Placebo / Placebo n=187 20% event rate	
Total	563	561	1,124

- If two medications are effective, we will have 80% power to detect a difference over placebo.
- If only one medication is effective, we will have 90% power to detect a difference over placebo.
- Assumes a 10% loss to follow-up rate.

These considerations result in a planned enrollment of 1,124 participants (187-188 in each arm). Because these sample size calculations are based on marginal tests, the actual power may be higher when based on the planned tests using adjusted logistic regression models adjusted for various predictive factors as described later.



12.3.1 Hypothesized Rates:

We hypothesize that metformin is superior to placebo for the primary endpoint controlling for possible use of fluvoxamine or ivermectin. Similarly, we hypothesize that fluvoxamine is superior to placebo for the primary endpoint controlling for possible use of metformin; and ivermectin is superior to placebo for the primary endpoint controlling for possible use of metformin. Let π_T and π_C denote the rate of the composite primary endpoint in the treatment and control groups, respectively. We will evaluate the following hypotheses:

$$H_0: \pi_T \geq \pi_C \text{ versus } H_A: \pi_T < \pi_C$$

The hypothesized marginal rate of the primary endpoint under placebo is 20%.[89] The expected event rate for the primary outcome in the single medication treatment arms is 11% which corresponds to a relative risk reduction of 45%. To detect this effect with 80% power using a marginal test with 5% two-sided type I error requires 337 participants in each comparison group. To account for effects of other drugs used in combination, which may reduce the event rate of the control group, for the interim analysis plan, and for losses to follow-up, we plan to enroll 1,124 participants in total.

Prespecified analyses:
A detailed SAP will be submitted to the DSMB and updated if needed prior to analyses. The primary efficacy analysis for each study drug, metformin, fluvoxamine, and ivermectin, will be based on a logistic regression model with a main effect for the relevant drug controlling for study site, and use of the other study drugs. In particular, no interaction effects will be included in this analysis. Prespecified subgroup analyses

include: pregnant women, and individuals who have already received a SARS-CoV-2 vaccine.

The SAP includes a sample-size re-calculation procedure that was pre-specified for the analysis of futility and efficacy on the first 2/3 of participants enrolled. This procedure was presented to and approved by the DSMB at the DSMB analysis of futility and efficacy done after 2/3 of participants were enrolled, + 14 days of follow-up. The updated total sample size for the study based on this sample size re-calculation is 1,350. This re-estimation accounts for a larger portion of participants being vaccinated and greater prevalence of monocloncal antibody use after enrollment than was envisioned when the protocol was written in fall 2020, and the resultant impact on the event rate in the placebo control arm; and external evidence from the Together Trial indicating a 33% relative reduction from fluvoxamine for which the original sample size would not provide adequate power.. The updated sample size is expected to provide 80% power to detect a 35% relative reduction from fluvoxamine, and similarly for ivermectin, while accounting for the recent impact of vaccination and therapeutics by using a projected estimate of the event rate for the primary outcome in the participants randomized to the placebo control arm.

12.4 DSMB Monitoring Guidelines:

Safety, efficacy and futility will be monitored for both cohorts by an independent DSMB (more info below). Timing of analyses will be with respect to information time defined as the proportion of participants who have completed the primary endpoint follow-up interval relative to the planned sample size. Interim analyses will include all participants who have been followed for specified window so as to exclude participants with possibly yet to be determined outcome status and thereby ensure unbiased estimates of the primary event rate in each arm. Safety data will be reviewed regularly by the DSMB. The first interim analysis of efficacy data (Stage 1) will focus on safety and feasibility, while still allowing early stopping for efficacy. Subsequent interim analyses of efficacy data (Stage 2) will focus on efficacy, futility and any ongoing safety or feasibility concerns.

12.4.1 Safety Monitoring:

Safety monitoring will be undertaken for each agent and combination. Regular reports will be provided to the DSMB at a mutually agreeable interval with an evaluation of safety outcomes that focus on comparisons of the frequency of deaths, SAEs and grade 4 events between the active treatment arms and placebo arm irrespective of attribution to study drug. Proportions and 95% exact confidence intervals will be used to summarize the results with unconditional exact tests and corresponding exact intervals to evaluate differences. Cumulative counts of adverse reactions and numbers of participants experiences and adverse reaction will be reported and compared similarly. Further safety assessments may be considered as demanded by the DSMB as well. The purpose of these reports is to catch any unexpected severe adverse reactions to metformin in the study populations. Formal statistical comparisons of safety endpoints using p-values will be undertaken at the request of the DSMB, and will otherwise not be reported.

12.4.2 Efficacy Monitoring:

Efficacy monitoring will be undertaken for each of the three active agents against its control. Efficacy monitoring boundaries will be based on a Kim and DeMets alpha-spending function that mimics O'Brien-Fleming boundaries (parameter value of 3). This upper boundary controls one-sided type I error at 2.5%, and will be modified according to the information fractions at the time of the actual analyses (defined by the current evaluable sample size / maximum sample size). The monitoring boundaries that will be provided to the DSMB for each cohort are reported in Table 2 and updated based on the actual sample size(s) available at the time of each analysis. The lower futility boundary will be treated as non-binding and supplemented with conditional power calculations in conjunction with the DSMB. This futility boundary is based on a Kim and DeMets beta spending function with a parameter value of 1.5. The lower Haybittle-Peto boundary for harm of -2.5 with 50% or less of the planned enrollment and -2.0 otherwise will be considered binding, though harm will be assessed in conjunction with safety data and may be declared by the DSMB despite the primary efficacy endpoint analysis not achieving this lower boundary. (Monitoring boundary calculations have been and will be carried out using the gsDesign package in R version 3.6.1 or newer.)

Following the sample size re-estimation procedure, the upper efficacy boundary will be calculated by spending the remaining type I error rate in proportion to the specified Kim and DeMets alpha-spending function where the information fraction is calculated with respect to the updated sample size. This approach corrects for over-spending alpha relative to the revised sample size and controls the overall one-sided type I error rate at the intended 2.5% level (or equivalently the two-sided 5% level).

Table 2: Monitoring Boundary Guidelines on Z-Score Scale. The futility boundary will be considered non-binding and supplemented by conditional power calculations. The harm boundary will be considered binding.

Sample Size	62	386	774	1,124
Efficacy	3.737	3.116	2.461	2.001
Futility	-2.130	-0.093	1.087	2.001
Harm	-2.500	-2.500	-2.000	-2.000

12.1 Sub-Study of Laboratory Outcomes:

The first approximately 62 to 82 patients will be analyzed as a sub-study to compare changes (from day 1 to days 5 and 10) in continuous laboratory outcomes between those on metformin to those on placebo (CRP, albumin, viral load, and microbiome changes (optional)), to help further understand mechanisms and apply for further funding early in the course of the trial.[65,66,90] The study procedures are the same for those in the sub-study as the rest of the trial.

12.2 Data Analysis:

A detailed SAP will be developed by the statisticians and included in the appendix prior to carrying out any unblinded data analysis of either cohort. Amendments to the SAP will be considered and developed by the blinded statistician(s). For secondary and tertiary outcomes, the unblinded statistician may participate in drafting amendments to the SAP but only for data for which their blind is not compromised. A brief analysis plan is outlined here. All analyses will

follow a modified intent to treat (mITT) principle, excluding participants who were post-randomization screen failures and who did not ingest any study drug. Formal comparisons will use 2-sided tests with a 5% significance level.

Descriptive statistics will be reported for baseline covariate information. Continuous variables will be summarized using mean and standard deviations, as well as median and interquartile range for skewed variables. Binary and categorical variables will be summarized using counts and percentages. Differences in important prognostic variables will be monitored visually with formal statistical testing undertaken only at the request of the DSMB.

Each study drug version control comparison will be separate. Each control group will consist of the participants who were eligible to receive the study drug but were assigned to a relevant placebo control arm instead. The metformin comparison will control for fluvoxamine and ivermectin use, and the fluvoxamine and ivermectin versus control comparisons will each control for metformin use. Primary hypotheses will be evaluated using logistic regression with a main effect for the relevant drug adjusted for study site and use of the other study drugs. The statistical significance of the main effect will be evaluated using a likelihood ratio test with interim monitoring boundaries specified above.

A secondary analysis for each study drug versus control comparison will control for age and BMI as well. Metformin effect heterogeneity with respect to biologic sex will be assessed in both cohorts though a logistic regression model with an interaction term, as well as separate logistic regression models fit to the data from males and females. During interim analyses, some participants will not have been followed adequately long for inclusion in the primary analysis. As a secondary analysis, marginal cumulative incidence rates in each arm at the specified follow-up interval will be estimated using the Kaplan-Meier method by censoring those in the midst of follow-up who have yet to experience the primary endpoint at their point of last study contact.

Laboratory outcomes, which are continuous longitudinally measured outcome, will be evaluated using generalized estimating equations with a treatment effect and adjustments for the corresponding outcome at baseline.

Secondary outcomes will be analyzed using generalized linear models with an appropriate distributional assumption and/or normalizing transformations. These analyses will adjust for study site and other prognostic information as appropriate. Time-to-event outcomes will be compared using Kaplan-Meier and log-rank tests as well as Cox proportional hazards models that adjust for prognostic variables. Ordinal endpoints will be analyzed using proportional odds regression models that adjust for prognostic variables and supplemented by logistic regression models for each ordinal threshold. These analyses will be supplemented by descriptive cumulative statistics for each ordinal category by treatment group. Detailed plans for primary, secondary and supplemental analyses will be provided in the SAP prior to conducting any unblinded data analyses.

All analyses will be carried out using R version 3.6.1 or newer.

12.3 Data Integrity:

The principal investigator will manage oversight of quality control for collected data. Recruitment of subjects will be performed using inclusion/exclusion criteria defined above Study data will be recorded within a REDCap database, which is HIPAA complaint, password protected

with variable assignable security access and an audit trail consistent with all regulatory requirements for maintenance of clinical trial data. Data summaries and quality control checks will be run routinely.

12.4 Missing Data:

Research coordinators will make a consistent effort to ascertain all study data within the protocol specified windows, as well as outside these windows as needed. Participants who fail to respond will be contacted by study staff multiple times, and family will be contacted as well, prior to being recorded as lost to follow up. All data collected on a participant prior to loss to follow up or withdrawal of consent will be included in analyses. Missing values will be multiply imputed using chained equations and predictive mean matching via the mice package and the effect estimate and confidence intervals will reflect the uncertainty in these missing values. For the primary outcome variables, sensitivity analyses that are biased towards the null will be carried out by assuming missing outcomes in the placebo arm follow the estimated distribution in the treatment arm, and vice versa for missing outcomes in the treatment arm. Additional details will be provided in the SAP.

13.0 Safety

13.1 Adverse Event (AE)

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study but does not necessarily have a causal relationship with study agent/intervention or procedures. Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

A clinical trial adverse event is defined as any untoward medical event associated with the use of a drug or study procedure. Non-serious adverse events will be collected during the period from enrollment (randomization) through the period on study drug, day 14. Any adverse event that is being collected as an expected Covid outcome by the Daily Covid Symptom Log or Clinical Outcomes assessments, or an expected side effect being collected by the Side Effect Survey, will only be recorded in those eCRF's and not additionally recorded in an adverse event eCRF. They will be reported to the DSMB at interim analyses.

Any adverse event that is not captured in the Covid Daily Symptom Log questions, Side Effect Survey, or Clinical Outcomes assessments will be recorded as an adverse event and reported to the DSMB at interim analyses. AE's will not be followed to resolution unless worsening during the course of the trial.

13.2 Serious Adverse Event (SAE)

Serious adverse events will be collected from enrollment through day 14 and 28. Investigators will determine if the event is serious or related to the study drug.

An SAE is any AE that is:

- Fatal,
- life-threatening,
- requires or prolongs a hospital stay,
- results in persistent or significant disability or incapacity,
- a congenital anomaly or birth defect, or
- an important medical event*.
  *Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent 1 of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

SAEs must be entered into the study database within 24 hours of investigator awareness of the event.

13.3 Assessment of Safety

Scale used to Grade Severity of Adverse Events. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials https://www.fda.gov/media/73679/download). The scale provides a grading severity scale for AEs with unique clinical descriptions of severity based on this general guidance, and for this study an ED visit (without hospitalization) is considered Grade 3, not Grade 4 (a hospitalization is Grade 4).

13.4 Investigator Assessment of Serious Adverse Events

The Investigator will evaluate all SAEs with respect to **Seriousness** and **Causality** (relationship to study agent and relationship to research) as defined below.

13.5 Causality

The likelihood that the SAE is related to the study agent will be assessed by the investigator considering the following categorization. Due to the severity of COVID-19 illness further detailed breakdown will not occur:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a

clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.
- Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study agent/intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- Not related: The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

13.6 Investigator Reporting Responsibilities:

13.6.1 Serious Adverse Events

All SAEs must be reported on the Serious Adverse Event case report form (SAE CRF) within 24 hours of awareness of the event. All other AEs must be reported within 5 business days of site awareness. The safety medical monitor will review all SAEs and determine the expectedness of each SAE.

13.6.2 Unanticipated Problems

An Unanticipated Problem is any event, incident, experience, or outcome that is

- unexpected in terms of nature, severity, or frequency in relation to
  - the research risks that are described in the IRB-approved research protocol and informed consent document; Package Insert, or other study documents;
  - the characteristics of the subject population being studied (persons with COVID-19); and
- possibly, probably, or definitely related to participation in the research; and
- places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problems will be reported in the study database. Unanticipated problems may include problems with protocol implementation, participant safety, and/or concerns regarding informed consent. Initial reports must be submitted within 7 calendar days of site awareness of the event.

13.7 Follow-Up of Serious Adverse Events

All unresolved SAEs will be followed by the CRC until the event is resolved or 14 days past the participants final study visit.

13.8 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions as defined in ICH E6 5.17 and as determined by the IND Sponsor will be reported to FDA, all participating country regulatory authorities, and all participating Investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA and all participating country regulatory authorities.

14.0 Data Monitoring

14.1 Data Integrity Monitoring

Data entry will be performed by trained members of the research team who have received documented delegation of authority. Data integrity will be overseen by the PIs and the statistical team. A study monitor will review the electronic consent documents, study drug administration data, and SAE reporting. Additionally, a random sampling of subjects will undergo full evaluation and comparison of source documentation with data entered into the study database if source documentation is needed. Source documentation will be collected according to each institution's requirements for source documentation.

The first data monitoring visit will be scheduled within an appropriate time after the first subject is enrolled, with subsequent visits thereafter at designated time intervals. Monitors will evaluate study team members to ensure access is consistent with training and delegation of authority logs.

Sites will maintain binders (either paper or electronic) containing pertinent documents and information including IRB approval letters, documentation of GCP training, licenses, human subjects research ethics training certificates, curriculum vitae, and correspondence.

14.2 Data Safety Monitoring Board (DSMB)

A data safety monitoring board (DSMB) has been convened and includes individuals meeting the key element criteria below, it includes a biostatistician with prior clinical trials experience. The DSMB will follow the guidance as outlined in the application and the DSMB charter unless there is a compelling, unanticipated reason to deviate from these rules. Data regarding the primary outcome will be reported to the DSMB at weekly intervals or according to the frequency decided by the DSMB. The DSMB may recommend stopping the trial early only for safety, following these guidelines:

A. Patient Safety

A recommendation to suspend, alter the study, or stop for harm would occur if the lower bound for harm is crossed at any interim analysis for the primary efficacy outcome, or there is concerning evidence in the opinion of the DSMB, there is concerning evidence in the opinion of the DSMB that the rate of IRB-reported SAEs is higher in the experimental group than in the placebo group.

Despite the lower number of formal preplanned analyses, the DSMB will still receive near timely reports of hospitalizations and deaths, and can deviate from this strategy and

perform earlier testing if desired. They retain authority to change this plan if the reporting suggests harm prior to the first formal planned assessment if they feel that a formal hypothesis test is warranted.

B. Efficacy

Efficacy monitoring will be monitored in accordance to the guidelines in Section 12.4.2.

The DSMB will operate in accordance with guidelines established by the FDA in "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committee" jointly published by the CBER, CDER and CDRH of the FDA (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees). The key elements include:

1. Expertise and independence: The members must have expertise in the area of study, not be study authors and have no financial conflict of interest.
2. Members will sign a confidentiality agreement.
3. It is preferred that the DSMB have a face-to-face initial meeting, but can meet by telephone thereafter more frequently.
4. All meetings must follow standard operating procedures (SOPs).

If the DSMB recommends closure of the study, then the DSMB Chair will email the principal investigator who will notify the IRB. If the trial is stopped for patient safety and a repairable cause of unacceptably high adverse events can be identified, the action must be reviewed and approved by the DSMB and IRB prior to resuming enrollment. For example, if one additional exclusion criterion is discovered that would account for the majority of unexpected events, this new exclusion criterion could be added, and the study could proceed.

14.3 Data Security:

All standard confidentiality procedures will be observed for this study. Research staff will be trained on protocol and GCP standards before they will be allowed contact with participants or data. All data will be stored in a secure HIPAA compliant manner. No indefinable data will be stored on individual research computers or flash drives.

15.0 Provisions to Protect the Privacy Interests of Participants

15.1 Protecting Privacy:

Conversations will be held in a private room whenever possible. Telephone calls will be performed one on one. The electronic consent process will take place using a REDCap program that is secure and HIPAA compliant.

15.2 Access to Participants:

Conduct of the study and determination of both safety and efficacy of the intervention requires access of the medical records. All study personnel undergo human subjects protection training and understand and value privacy standards set forth by HIPAA. Participants enrolled in the trial are made aware during the informed consent procedure that study personnel will be required to

access this private information for trial conduct, and consent to this access prior to agreeing to participate.

16.0 Compensation for Research-Related Injury

16.1 Compensation for Research-Related Injury:

The sponsor does not have funds for research-related injury compensation.

16.2 COVID-19 PREP Act

Due to the coronavirus public health crisis, the federal government has issued an order that may limit your ability to recover damages if you are injured or harmed while participating in this COVID-19 clinical study. If the order applies, it limits your ability to recover damages from the University, researchers, healthcare providers, study sponsor, manufacturer or distributor involved with the study. However, the federal government has a program that may provide compensation to you or your family if you experience serious physical injuries or death due to this study. To find out more about this "Countermeasures Injury Compensation Program" go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

17.0 Multi-Site Research

17.1 Study-Wide Number of Participants:

Up to 1,160 participants will be enrolled in the study to achieve the needed number of completed data sets.

17.2 Study-Wide Recruitment:

Each site will determine appropriate recruitment methods. A study brochure will be made available to all sites. Coordinators from the central site may help call positive patients at participating sites if a site becomes overwhelmed at any given time, given the rapidly changing geographic nature of this pandemic.

17.3 Communication with Sites:

All sites will be given access to study documents through the University of Minnesota BOX.

A project manager will be tasked with coordinate all communication, regulatory efforts, and ensuring sites are informed of study changes. The Project Manager will also work with the PI to ensure all non-compliance, adverse events, and other reportable events are reviewed and reported in accordance with local policies.

All study data will be entered into REDCap with each site being assigned a specific data access group so that staff at one site cannot see participant data from another site.

Personnel from all sites will participate in monthly progress meeting calls, which will include discussion of any problems including reportable events, interim results, and completion of the study. More frequent meetings may be planned, as necessary.

18.0 Appendices

19.0 References

1.0

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