A Randomized, Double-Blind, Comparative Trial of the Safety and Efficacy of Famotidine vs Placebo for the Treatment of Non-Hospitalized symptomatic Adults with COVID-19

Northwell Health HRPP:

IND #: 152331

PROTOCOL VERSION: 10

June 8, 2021

National Clinical Trial (NCT) Identified Number: NCT04724720

Principal Investigator: Tobias Janowitz, MB, BChir, Ph.D, Cold Spring Harbor Laboratory

Sub-investigators: Joseph Conigliaro, MD, MPH, Northwell Health, Christina Brennan, MD, MBA Northwell Health; Sandeep Nadella, MD (Northwell Health and Cold Spring Harbor Laboratory)

Trial Management Group (TMG): David Tuveson, MD PhD (Cold Spring Harbor Laboratory); Jie Yang, PhD statistics (Stony Brook University);

Sponsor: Northwell Health

Funded by: Fast Grant and Pershing Square Foundation

Proprietary and Confidential

Table of Contents

PROTOCOL SYNOPSIS

1. INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, China, on 31 December 2019. The World Health Organization (WHO) declared the outbreak a global health emergency on 30 January 2020. Based on current epidemiological investigations, the post-exposure incubation period prior to onset of COVID-19 symptoms is one to 14 days, and typically ranges from three to seven days. In 80% of patients, COVID-19 presents as mild disease, but is still associated with significant "silent" viral shedding and infectivity.[1] 20% of cases develop severe (13%) or critical (6%) illness.[2] More severe forms of COVID-19 present as clinical severe acute respiratory syndrome, but include a T-predominant lymphopenia, high circulating levels of proinflammatory cytokines and chemokines, accumulation of macrophages and neutrophils in lungs, and immune dysregulation including immunosuppression.[3] SARS-CoV-2 is highly infectious, and a minimal infectious dose has been estimated at 10 to 1000 viral particles. Infection can be transmitted by direct interpersonal contact, fomites, respiratory secretions, and direct viral shedding into the air via normal respiration. SARS-CoV-2 has been isolated from both feces and urine. As of July 25th 2020, the US has reported nearly 4.2 million cases and nearly 150,000 dead. In New York State there are over 415,163 confirmed cases with over 32,000 deaths.

The treatment for COVID-19 remains unclear. There are no definitive vaccine, therapeutic antibody, or antiviral drug medical countermeasures currently authorized by the FDA for prevention or treatment of mild to moderate COVID-19 disease. For hospitalized patients, antiviral treatment with remdesivir or with dexamethasone in addition to supportive care supplemented by oxygen and active ventilatory support for critical cases have shown benefit.[4–6]

Since we conceived this study, several treatment options for mild to moderate COVID-19 have recently received emergency use authorization. These are the combination antibodies: Casirivimab plus Imdevimab and the single antibody from Eli Lilly, Bamlanivimab.[7] Four vaccine candidates are currently undergoing testing in the United States: these are being developed by Sanofi/GlaxoSmithKline, Moderna, Oxford/AstraZeneca and Jannsen Pharmaceuticals. The latter three are currently in phase 3 trials.[7] Pfizer and Moderna have applied for emergency use authorization for their vaccine candidates. However, these treatments are not expected to be widely available to all patients until a few months and new viral variants are now emerging that may not be effectively protected against by current vaccines. A recent report by the Center for Disease Control (CDC) states that approximately one third of patients with COVID-19 in an ambulatory setting do not return to usual health within 2-3 weeks.[8] Famotidine may be a candidate medication for this setting to alleviate the symptoms and shorten the symptomatic period in this population. Famotidine is a histamine-2 receptor antagonist, widely available over-the-counter and at low cost, and is safely used for suppression of gastric acid production over a wide range of doses from 20mg once daily to 160mg four times daily.[9] In computer-based simulations, Famotidine had been identified as a potential inhibitor of the 3-chymotrypsin-like protease ($3CL^{pro}$)[10], but biochemical investigations have demonstrated no binding or active side inhibition of this or the papain-like protease of SARS-CoV-2.[11] With regard to clinical studies a propensity score matched retrospective cohort study a significantly reduced risk for death or intubation (adjusted hazard ratio 0.43, 95% confidence interval 0.21-0.88) was identified for patients

with COVID-19 who were taking Famotidine before or at the point of hospital admission.[12] Furthermore, another retrospective, propensity matched observational study of 878 patients tested positive for COVID-19 found famotidine to be associated with a decreased risk of in-hospital mortality and combined risk for death or intubation. In addition, patients that took famotidine showed lower inflammatory markers (CRP, Ferritin, Procalcitonin) than those patients that did not take famotidine.[13] In addition, a case series of 10 patients with COVID-19 who self-medicated with oral famotidine, significant improvement of symptoms was associated with famotidine use after 24-48 hours.[14] These effects were noted in patients who mostly took doses of 80mg three times daily suggesting that famotidine's action is either through its main known high affinity target, the histamine type 2 receptor (H2R) or through combined inhibition of histamine receptors. A mechanism by which famotidine may work, is through reduction of H2R signaling on monocytes and therefore biased differentiation to dendritic cells and reduced differentiation to macrophages, with a resulting reduction of immune overactivation and cytokine release.

1.1 Background

Clinical presentation: COVID-19 frequently presents with a range of symptoms such as fatigue, dry cough, shortness of breath, headaches, and loss of smell or taste. Nasal congestion, runny nose, sore throat, myalgia and diarrhea are found in some cases.[15,16] Fever is one of the presenting signs of COVID-19. Patients with severe disease often develop dyspnea and/or hypoxemia after one week. In severe cases, patients may progress rapidly to acute respiratory distress syndrome (with classic ground glass radiographic findings), septic shock, metabolic acidosis that is difficult to correct, coagulopathy, cytokine storm and multiple organ failure. Severe and critically ill patients may present with moderate to low fever or may even be afebrile.[17]

Symptom tracking in COVID-19: Patient recorded outcome measures (PROMs) are an important tool in medical research. They include information on symptom severity scores, which have been used in other clinical syndromes and are a common method to track disease progression in routine patient care and clinical trials about Rheumatoid arthritis[18] and inflammatory bowel disease[19]. Janowitz and colleagues developed a symptom score based on the Eastern Collaborative Oncology Group performance status scale, which was initially developed for patients with cancer diagnoses.[20] In a case series[14] symptom scores for general unwellness, cough, shortness of breath, fatigue, headaches, and loss of taste or smell (anosmia) were retrospectively reported by patients on an ordinal scale: 1 = not affected, 2 = little affected, 3 = affected, 4 = severely affected. The symptoms were chosen from a list of NIH endorsed symptoms for COVID-19 patient reported outcome[15]. When the changes of the normalized total symptom score across all patients were analyzed, Janowitz et al. found that a significant improvement in the symptom score was reported within 24 hours of starting Famotidine and that symptoms continued to improve and nearly normalized to pre-illness levels at 14 days after the first Famotidine use.[14] The improvement of symptoms was across all categories, but airway related symptoms such as cough and shortness of breath were reported to improve more rapidly than systemic symptoms such as fatigue. In addition to the case series by Janowitz et al., there is further evidence about the benefit of symptom tracking in patients with COVID-19: Most importantly, the guide for COVID-19 treatment research published by the Food and Drug Administration (FDA)[21], lists sustained clinical recovery measured by resolution of symptoms as a suitable primary endpoint, equally prioritized as hospitalization and mortality. Furthermore, it has been shown that in COVID-19, patient reported symptom severity is predictive of disease duration in non-

hospitalized patients[22] and patients can reliably transmit symptoms longitudinally.[16] In this study, we will assess symptom severity longitudinally and in concordance with the FDA guidelines[21,23] and we refer to this activity as "symptom tracker". Patients also record other measures and the overall umbrella abbreviation PROMs is used when other measures or a combination of symptom tracker and other measures are referred to.

Laboratory tests: In the early stages of the disease, peripheral WBC count is normal or decreased with decreased lymphocyte count. Some patients develop elevated liver enzymes, ferritin, muscle enzymes and myoglobin. Elevated troponin is seen in some critically ill patients, while most patients have elevated C-reactive protein, erythrocyte sedimentation rate and procalcitonin. In severe cases, the D-dimer increases and peripheral blood lymphocytes progressively decrease. Severe and critically ill patients often have elevated inflammatory factors and cytokine levels, but the degree of elevation in mildly to moderately ill patients is not known. Development of lymphopenia (pan T-cells) often corresponds with deteriorating respiratory function requiring ventilatory support, and a trend towards resolution of lymphopenia may predict recovery and transfer from ICU to more traditional inpatient supportive care. The value of laboratory tests for management of non-hospitalized patients is not known and an important research question.[24–26]

Viral detection: SARS-CoV-2 nucleic acid can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces and other specimens using RT-PCR methods. Detection of viral nucleic acid may be more accurate if specimens from lower respiratory tract (sputum or air tract extraction) are tested. The specimens should be submitted for testing as soon as possible after collection. The value of viral detection tests for management of non-hospitalized patients is not known and an important research question.[27]

Physiological and activity monitoring: Fever, hypoxia, decreased lung function and reduced activity levels are associated with mild to moderate COVID-19. These can be monitored and recorded in an outpatient setting using standard thermometers, peripheral oxygen saturation measurements, and activity monitoring devices.[28]

1.1.1 *Pharmaceutical and Therapeutic Background*

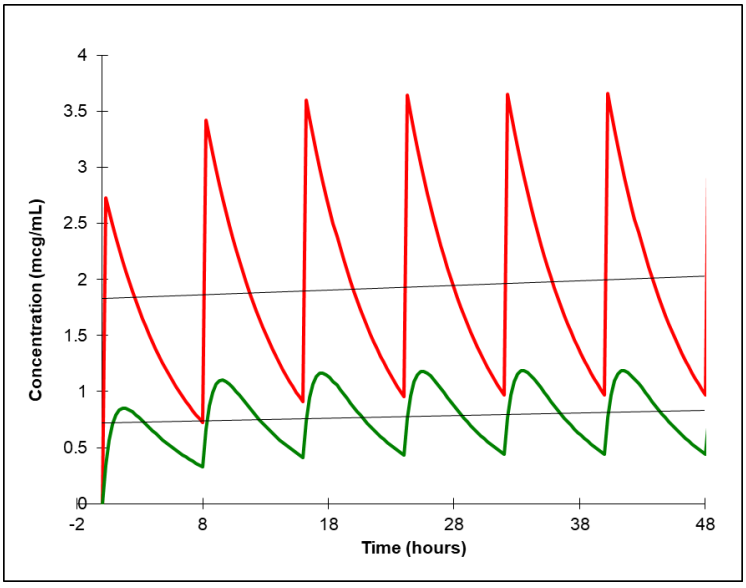
There is an urgent need for an effective treatment to treat symptomatic patients but also to decrease the duration of virus transmission in the community. Among candidate drugs to treat COVID-19, repurposing of FDA-approved drugs for use as antiviral treatments is proposed because knowledge on safety profile, side effects, and drug interactions are well known.

Famotidine (Pepcid), a histamine H2 antagonist widely available over-the-counter has a favorable pharmacokinetic and safety profile, with no known significant drug-drug interactions, and a very wide therapeutic window. Famotidine was originally formulated for gastric acid suppression to assist with healing gastrointestinal ulcers and was given FDA approval for this purpose in 1995 as part of a formulation called Pepcid. Famotidine is typically used at either 40 mg or 80mg/day for acid suppression. It is available as part of several over the counter preparations at this dosing. Famotidine has a potential drug-drug interaction with Tizanidine. Therefore, Tizanidine will be excluded as a permissible concomitant medication for patients enrolled in this trial.

Pharmacokinetics: Famotidine is known to possess linear pharmacokinetics. The oral bioavailability of famotidine is 40-45 %. Figure 1 shows the pharmacokinetic simulations based on IV and oral product prescribing information pharmacokinetic parameters at 20 mg twice daily dosing, which is the over-the-counter dose. Anecdotal case studies suggest clinical benefits associated with administration of famotidine at over-the-counter doses in mild COVID-19 infection. More recently, retrospective data released out of Columbia University Medical Center showed that use of famotidine was associated with reduced risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80) irrespective of the dose taken. After balancing baseline patient characteristics using propensity score matching, these relationships were unchanged (HR for famotidine and death or intubation: 0.43, 95% CI 0.21-0.88).[12] Similar results have been found in a second independent study of the same method.[13] Additionally, a case series of 10 patients who self-administered Famotidine, most frequently at a dose of 80 mg po TID, but across a dose range from 20 mg po TID to 80mg po TID, demonstrated an association of Famotidine use with an improvement in symptoms scores [Figure 2]. [14]

Detailed studies of famotidine affinity to the H2R indicate a binding constant (Kd) of approximately 10 nM.[29] The pharmacokinetic simulations suggest that a dose of 20mg po BID achieves a steady-state trough level of 0.02 mcg/ml, corresponding to a molar concentration of 60 nM. Therefore, the approved over-the-counter dosing regimen of 20mg po BID may be sufficient to achieve near complete H2R occupancy, but other histamine receptors may also be relevant and not inhibited at that concentration. The combined inhibition of the histamine receptors could change activation of monocytes, which we believe may be the main cells that drive the immune overactivation that causes the systemic unwellness in patients with COVID-19. At a dose of 80mg PO TID, the steady-state plasma trough level would be 0.44mcg/ml corresponding to 1.2 microM, a concentration at which the other histamine receptors may also be blocked by famotidine.

Taken together, the evidence that 80mg PO TID is safely tolerated, achieves a realistic plasma level for histamine receptor blockade, and has been shown in the case series to be associated with a safe reduction in symptoms of patients with mild to moderate COVID-19, argues that this should be the dosing regimen used in the randomized double blinded outpatient study.



80mg PO dose TID	IV	Oral
Peak steady-state (mcg/mL)	3.83	1.19
Trough steady-state (mcg/mL)	0.97	0.44
Tmax steady-state [h]	0.00	1.48
Cave (mcg/mL)	2.08	**0.83**
ke [1/h]	0.171	0.171
ka [1/h]	6931	1.386
t1/2(el) [h]	4.04	4.04
Fluct. [%]	137.1	89

Figure and Table 1: Simulated pharmacokinetics of Famotidine. Famotidine is known to possess linear pharmacokinetics[30–32]. The information above are pharmacokinetic simulations based on the IV and oral product prescribing information pharmacokinetic parameters at 80 mg TID dosing. The information above is not data from human studies.

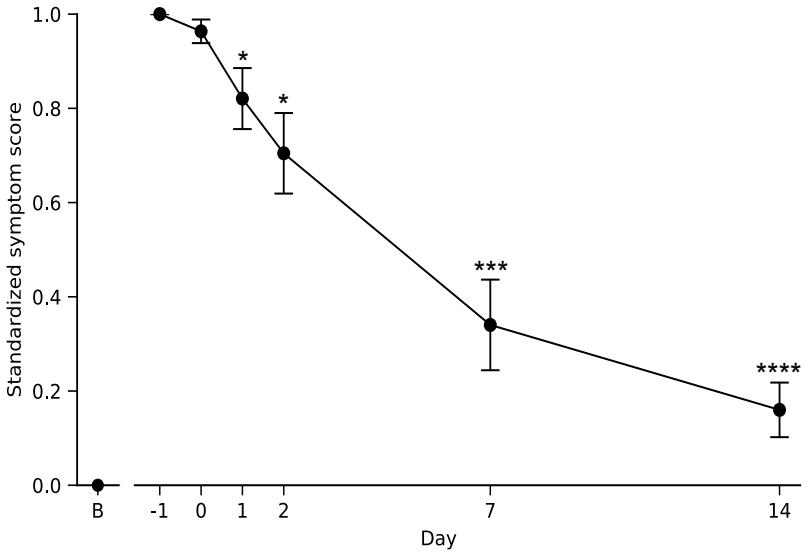


Figure 2. Normalized symptom scores of all patients. The mean longitudinal normalized symptom score for all patients is shown. The standard error of the mean is indicated. Statistical comparisons by t-test in comparison to day 1, the day of starting Famotidine. *, p<0.05; ***, p<0.001; ****, p<0.000. From Janowitz et al.[14]

1.2 Study Rationale

To reduce global morbidity and mortality effective treatment strategies for non-hospitalized patients are required. Famotidine is widely available over-the-counter at low cost, does not interact with other medications, and has been safely used for suppression of gastric acid production over a wide range of oral doses from 20mg once daily to 160mg four times daily. Blocking the Histamine receptor type 2 on monocytes could reduce the immune-overreaction and thereby alleviate symptoms (unpublished preliminary results, T. Janowitz and K. Tracey). In a retrospective propensity scored cohort study, famotidine use coincided with reduced mortality and morbidity in hospitalized patients[12,13]. In a case series of non-hospitalized patients with COVID-19, famotidine was well tolerated when taken orally at doses up to 80mg TID and was associated with rapid symptomatic improvement[14]. These findings support the implementation of a randomized double blinded placebo-controlled study that investigates efficacy

of famotidine in the treatment of non-hospitalized patients with COVID-19. Furthermore, this study could provide evidence that tracking symptom severity with e.g. the "COVID-19 symptom score" is a sensible and reliable instrument to differentiate the effect of a study drug compared to the normal course of the disease.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1 Study Objectives

2.1.1 *Primary Objective*

The overall objective of the study is to evaluate the clinical efficacy of COVID-19 treatments consisting oral famotidine vs placebo in symptomatic non-hospitalized patients with confirmed COVID-19. This will be assessed by monitoring clinical recovery, which corresponds to a total, unweighted COVID-19 symptom score of ≤3 for two consecutive days. This primary endpoint was chosen in concordance with the FDA guidelines and because no other validated endpoint for outpatient studies exists to date.[21] We will assess quantification of resolution of symptoms using the "COVID-19 symptom score". This score will be derived from the answers to a questionnaire based on the NIH endorsed guidelines[15] and the recent FDA guidelines for studying COVID-19 in an outpatient setting[23] and a shorter version has been utilized as a scoring system in the case series by Janowitz et al.[14] 17 symptoms (fatigue, shortness of breath, loss of taste or smell, headache, cough, sore throat, hoarse voice, runny/stuffy nose, difficulty breathing, chest pain, abdominal pain, diarrhea, nausea, dizziness, loss of appetite, eye soreness, and muscle aches) will be graded daily on an ordinal scale from 0 to 3. In addition to the FDA guidelines, we consider a reduction of the "COVID-19 symptom score" to be a suitable primary objective as tracking symptom severity is well established and reliable in treatment assessment and clinical trials for other diseases of immunological etiology.[18,19]

2.1.2 *Secondary Objectives*

Comparisons across the two treatment arms will be made with the objective to assess:

1. Clinical recovery by day 60
2. Longitudinal COVID-19 symptom scores
3. Safety and tolerability of the intervention
4. Clinical Progression
5. Comparing severity of inflammatory response
6. Assessment of ventilation and perfusion using peripheral oxygen saturation
7. Time to resolution of individual symptoms
8. Difference in 28-day Mortality
9. Comparing proportions of patients having been hospitalized

2.1.3 *Exploratory Objectives*

Comparisons across the two treatment arms will be made with the objective to assess:

1. Change in pulmonary function

2. Change in blood markers indicative of immunological function of the patient and severity of the inflammation
3. Longitudinal change in body weight
4. Longitudinal change in body temperature
5. Symptoms of COVID-19 that were not included in the initial "COVID-19 symptom score"
6. Clearance of viral RNA of Sars-CoV-2
7. Production of Antibodies against SARS-CoV 2
8. Change in activity measures
9. Quantitative intake of drugs aimed at alleviating symptoms of COVID-19 other than Famotidine
10. Length of Stay (LOS) if patient gets hospitalized
11. Detection of viral variants

2.2 Hypothesis

The working hypothesis is that famotidine will alleviate symptoms of COVID-19 in patients with mild or moderate disease. This will be tested by comparing the efficacy of famotidine to placebo.

2.3 Study Endpoints

2.3.1 *Primary Efficacy Endpoint*

The primary endpoint is cumulative incidence of symptom resolution at day 28. Time to symptom resolution will be defined as the number of days after randomization to the first time that total COVID-19 symptom score is ≤3 and no symptom having a score >1 for two consecutive days. It is unlikely that given our planned enrollment of 84 patients, we would encounter patients who obtain a symptom score consistent with resolution followed by clinical deterioration. Studies utilizing similar symptoms scores have not reported worsening symptoms after defined resolution.[33,34] The symptoms will not be weighted in this analysis. For patients who will not achieve symptom resolution, their time to symptom resolution will be censored at day 28. Death without symptom resolution will be treated as a competing risk event. However, very few deaths are expected in our enrolled patients.

2.3.2 *Secondary Efficacy Endpoint*

1. The relative change in the COVID-19 symptom score from baseline (Day 0 before taking any medication) to Day 28, defined as the rate of change will be assessed.
2. Cumulative incidence of symptom resolution at day 60
3. The relative change in the COVID-19 symptom score from baseline (Day 0 before taking any medication) to Day 7, defined as the difference of Day 7 total symptom score and baseline symptom score (Day 0 total symptom score) divided by baseline symptom score will be assessed.
4. Assessment of Serious Adverse Events.
5. Clinical Improvement of subject (9-point ordinal scale) as recommended by the WHO for clinical trials about COVID-19:[35]

Score	Patient state	Descriptor
0	Uninfected	No clinical or virological evidence of infection
1	Ambulatory	No limitations of activities
2	Ambulatory	Limitations of activities
3	Hospitalized – mild disease	Hospitalized, no oxygen therapy

4	Hospitalized – mild disease	Oxygen by mask or nasal prongs
5	Hospitalized – severe disease	Non-invasive ventilation or high-flow oxygen
6	Hospitalized – severe disease	Intubation and mechanical ventilation
7	Hospitalized – severe disease	Ventilation + additional organ support – pressors, RRT, ECMO
8	Dead	Death

6. CRP, procalcitonin, and ferritin levels in isolation or combination on Day 7 compared to Day 1
7. Peripheral oxygen saturation on Day 7 compared to Day 1
8. Cumulative incidence of resolution (symptom score decrease to <=1) of each individual symptom that are >1 at baseline listed in the extended COVID-19 symptom score
9. 28-Day Mortality
10. Proportions of patients having been hospitalized by Day 28

2.3.3 *Exploratory Efficacy Endpoint*

Note: Day 14 and Day 28 blood tests will to be optional from 03/10/2021 and this may result in reduced ability to report the relating exploratory enpoints.

1. Pulmonary function using spirometry (including but not restricted to peak expiratory flow and forced vital capacity)
2. Change on Days 7, 14, 28 compared to Day 1 of:
    a. Hematological markers (including but not restricted to Immune cell activation, of WBC fractions, i.e. neutrophils, monocytes, macrophages, B- and T – lymphocytes, eosinophils, platelets)
    b. Organ function, including estimated glomerular filtration rate, AST, ALT, bilirubin, albumin, and coagulation panel
    c. Inflammatory markers (including but not restricted to histamine)
    d. Change in d-dimer
    e. Plasma Famotidine Levels
    f. Expression profiles in Leukocytes analyzed by including but not limited to RNA sequencing analysis. This analysis will be performed at Cold Spring Harbor Laboratory.
3. Longitudinal daily change in body weight on
4. Longitudinal body temperature
5. Virologic response as measured by percent change in PCR copy number on Day 7, Day 14, and 28 relative to enrollment Day 0.
6. Production of Antibodies against SARS-CoV 2: Measurement of Antibodies on Day 1 and Day 28
7. Change in activity measurements acquired via a fitness tracker including but not restricted to resting heart rate, walking distance equivalence and estimated energy expenditure.
8. Quantitative intake of drugs aimed at alleviating symptoms of COVID-19 other than Famotidine, including but not restricted to analgesics, antipyretics, and over-the-counter cough medicine
9. Length of Stay (LOS) if patient becomes hospitalized (number of days from admission to discharge)
10. Physiological parameters automatically captured by spirometer, pulse oximeter and thermometer that might inform disease severity.
11. Analysis of viral variants in relation to endpoints

3. STUDY DESIGN

3.1 Overall Design

Phase 2 Randomized Double-Blind Placebo Controlled Trial

3.1.1 *Study Duration*

The study is expected to last for up to six months. We expect the screening and enrollment period to last for up to five months since the availability of antibodies may hinder our enrollment.

3.1.2 *Duration of Study Participation*

An individual subject will complete the study in about 60 days, from screening at Day 0 to the last follow up on day 60. Pregnant women enrolled into this study will be followed up until 12 months after the estimated due date.

4. STUDY POPULATION

4.1 Inclusion Criteria

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Adult ≥18 years of age at time of enrollment.
4. Subject consents to randomization.
5. Subject has confirmed COVID-19 disease < 72 hours prior to randomization
6. Subject has been experiencing symptoms for >1 day but ≤7 days
7. Able to use an electronic tablet and Bluetooth devices.
8. Subject has mild to moderate COVID-19 which is defined as (equivalent to 1,2 on WHO scale):
   a. Patient does not require immediate admission to the hospital within 24h of initial assessment
   b. Patient does not require supplemental oxygen due to COVID-19
   c. Patient has a score of 2 (“moderate”) in at least 3 of the symptoms in the COVID-19 symptom score

4.2 Exclusion Criteria

- Any exposure to investigational medications targeting COVID-19 during the present disease. These include recently approved antibodies (passive immunization) for treatment of COVID-19.
- Use of famotidine within the last 30 days for any indication, e.g. medicating gastric ulcer or recent off label use for COVID-19.

- Severe COVID-19 disease at time of enrollment requiring admission to hospital
- History of Stage 3 severe chronic kidney disease, i.e. eGFR of < 60ml/min
- Allergy to famotidine or non-medical ingredients of the study tablet
- Known to be immunocompromised by treatment for existing disease due to the immunomodulatory effects of famotidine and therefore possible effects on the pre-existing disease or the immunosuppressive therapy
- Patients currently using tizanidine
- Documented deficiency of any of the following minerals: Al, Cu, Mn, Fe and Zn
- Inability to perform the tasks required for the patient reported outcome measure recordings, including but not restricted to limited language proficiency.
- Have symptoms of dysphagia or inability to swallow size #000 capsules.

4.2.1 *Rationale for Selected Exclusion Criteria*

Famotidine is overall well tolerated but in the case of renal insufficiency the risk of prolongation of the QT interval is increased. Patients taking immunosuppressive medication to treat preexisting disease will be excluded from the trial. This is due to the potential immunomodulatory effects of famotidine and therefore possible effects on the pre-existing disease or the immunosuppressive therapy.[36]

4.3 Study sites

This clinical trial will be conducted at Northwell Health on Long Island, New York in the outpatient setting and the division of general medicine. Many of the clinical protocols that are standard of care conform to this study's protocol.

5. STUDY TREATMENTS

5.1 Stratification, Randomization, and Blinding

5.1.1 *Stratification*

Prior to randomization, subjects will be stratified by Gender (M/F), and age group (<60/≥60), .

5.1.2 *Randomization*

This study is a Phase II randomized, double blinded, placebo controlled trial to evaluate the safety and efficacy of 80 mg of oral famotidine three times daily in comparison placebo in non-hospitalized adult patients diagnosed with COVID-19. The study will be conducted in neighborhoods of hospitals within the Northwell Health system in New York, United States.

Randomization will be carried out using a balanced 1:1 permuted block design with block sizes 2,4,6.

The Biostatistics Unit will develop and implement the randomization procedure using the Biostatistics Randomization Management System (BRMS). The Biostatistics Randomization Management System (BRMS) is a secure, HIPAA-compliant, web-based application that allows investigators to randomize

subjects into randomized clinical trials (RCTs) using their personal computer. The BRMS allows for multi-center, stratified, and single/double blinded RCTs, using permuted blocks. Randomization notifications (respectful of blinding status) are automatically sent to the PI and other authorized personnel. BRMS includes a feature that allows for medically indicated breaking of the blind, with requirement for justification. BRMS includes an audit trail of all transactions.

5.1.3 *Blinding*

Upon determining eligibility, the assigned study coordinator will utilize the BRMS randomization system to randomize the subject. An unblinded study staff member will be automatically notified by BRMS via email that a subject has been randomized and the identity of the treatment arm will be made known to the staff member.

Qualified study personnel will supply the patient with famotidine or placebo for oral self-administration. Specific instructions for managing the investigational products will be provided. There will be a placebo tablet. Participants randomized to the placebo arm will receive placebo tablets, hence all participants will receive medication regardless of what arm of the study they are being enrolled in. The drug must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and subjects. Study subjects, the principal investigators, and study site personnel, except unblinded study staff member will remain blinded to all randomization assignments throughout the study. The Study Director, Study Monitor, and any other study personnel who are in regular contact with the study site will remain blinded to all subject randomization assignments. The study team members directly involved with study conduct will be blinded. Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review.

5.1.4 *Emergency Unblinding Procedure*

BRMS includes a feature that allows for medically indicated breaking of the blind, with requirement for justification. User logs onto BRMS and clicks the "break the blind" icon and follows instructions. The blinding may be broken under the following circumstances:

a. Suspected serious adverse event of study medication that require reporting to the FDA or when breaking the blind is deemed essential for patient's medical care.

b. To determine eligibility of an enrolled subject for another clinical trial if they become critically ill from COVID-19.

5.2 Study Drug(s)

To ensure blinding and indistinguishability of the study drug vs. placebo, we pursued an over-encapsulation strategy (see photograph below of a sample size #000 opaque capsule). We will have the study drug and placebo over encapsulated as follows:

1) Active capsules: 4x20 mg Famotidine tablets (manufactured by Alchem) in a size #000 white, opaque, capsule (Capsugel). (See Appendix I) 50 capsules per bottle in a 120ml white HDPE bottle with heat induction seal and childproof lid. A capsule is being used to overcome any risk of contaminated gelatin.

a) Famotidine (ANDA 077351) to be over-encapsulated will be obtained from either Kirkland or Equate brands currently sold over the counter in the USA.
   i) Following is their detailed information from the US FDA Orange book:
      (1) Product Details for ANDA 077351
      FAMOTIDINE (FAMOTIDINE)
      20MG
      Marketing Status: Over-the-counter
      Active Ingredient: FAMOTIDINE
      Proprietary Name: FAMOTIDINE
      Dosage Form; Route of Administration: TABLET; ORAL
      Strength: 20MG
      Reference Listed Drug: No
      Reference Standard: No
      TE Code:
      Application Number: A077351
      Product Number: 001
      Approval Date: Sep 25, 2006
      Applicant Holder Full Name: PERRIGO R AND D CO
      Marketing Status: Over-the-counter

2) Placebo capsules: Avicel (FMC Corporation, PA), USP in a size #000 white, opaque capsule (Capsugel). See Appendix I 50 capsules per bottle in a 120ml white HDPE bottle with heat induction seal and childproof lid. . Please see Appendix I for details on certificate of quality for Avicel.

The drug supply, placebo and test capsules are being procured by Alchem Laboratories Corp. 13305 Rachael Boulevard, Alachua FL 32615.

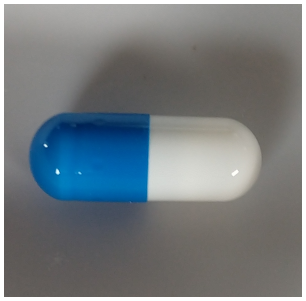


Figure 3: Example picture of a size #000 opaque capsule used for over-encapsulated placebo .

i. Study drug description

The active ingredient in PEPCID® (famotidine) is a histamine H2-receptor antagonist. Famotidine is N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene) amino]-4 thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is C8H15N7O2S3 and its molecular weight is 337.43.

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each capsule for oral administration contains 4 tablets of 20 mg each of famotidine (total of 80mg famotidine per capsule) and the following inactive ingredients: hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycolate, sodium starch glycolate, modified corn starch (pregelatinized starch), talc, triacetin, and titanium dioxide. The placebo capsules are similar in composition but filled with Avicel (FMC Corporation, PA). Avicel is a cellulose product which will serve as inert ingredient in the placebo capsules. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric juice secretion. Famotidine reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretions. Famotidine and other H2 antagonists, including cimetidine and ranitidine, have been documented as having potent antiviral activity against Human Immunodeficiency Virus. The immunomodulatory effects of H2-receptor blocking could alleviate the symptoms and might even prevent damage from Histamine-mediated immune-overreaction.

ii. Administration

The study will investigate oral doses of famotidine given at doses within the range of clinical practice. The total daily dose proposed in this study will be 240 mg/day famotidine p.o. for a maximum of 14 days, or until hospital admission, whichever comes first.

iii. Storage

Store study drug at 20°C to 25°C (68°F to 77°F). Protect from light.

iv. Pregnancy and breastfeeding women

All pregnant and lactating women enrolled in the study will be done under the guidance of Northwell Obstetrics/Gynecologist Dr. Gary Goldberg. Briefly, when such subjects are encountered, they will presented and discussed in detail with Dr. Goldberg or his team prior to enrollment as long as it felt safe to do so. The benefits of treatment with famotidine should be weighed against potential risks by the health care team. While the evidence is not sufficient, there have been few studies suggesting that H2-Antagonists were not associated with congenital malformations, prematurity, low birth weight, or perinatal mortality.[37] Pregnant women will therefore not be excluded from the trial, but adequately educated about the lack of studies proving safety of famotidine use during pregnancy and the fact that the daily dose in this trial is six times the FDA-recommended over-the-counter dose.

In concordance with the FDA regulations regarding studies with pregnant women,[38] we will follow up with women who are pregnant while taking famotidine for up to 12 months after the estimated due date. For further clarification see section 8.1.

We will not exclude breastfeeding women from this trial, as peak milk levels of famotidine are lower than doses of famotidine administered to newborn infants for other indications.[39] We educate breastfeeding women about this situation properly.

v. Adverse Reactions

Famotidine is usually well tolerated; most adverse reactions have been mild and transient. The following adverse reactions have been reported at a rate greater than 1% in patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: headache

(4.6%), dizziness (1.2%), constipation (1.2%) and diarrhea (1.6%). The following additional adverse reactions have been reported since the drug was marketed: urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema. Toxic epidermal
necrolysis has been reported very rarely with H2-receptor antagonists. As with other H2-receptor antagonists, cases of bradycardia, A-V block and other arrhythmias have been reported rarely in patients treated with famotidine. Gynecomastia has been reported rarely. In most cases that were followed up, it was reversible after treatment was discontinued. Famotidine in some case studies is QT prolonging (most in renal failure) and has been noted to prolong QT at usual dose.

Decreased kidney function: Famotidine is unlikely to be causal, but we recognize that in COVID-19 patients the development of renal insufficiency is not uncommon and can lead to an increase in other AEs. Risk of delirium with H2 blockers especially high dosage is most associated in the setting of renal dysfunction.[9]

Absorption reducing effects of famotidine: Since one of famotidine's primary mode of action is on suppressing gastric acid secretion via blocking histamine signaling in the parietal cells of the stomach, we expect that our study population receiving famotidine will have a significant increase in their gastric pH compared to those receiving placebo. This may affect absorption of divalent cations including Al, Cu, Mn, Fe and Zn.[40] Hence patients with documented deficiencies of these minerals who are on oral replacement therapy will be excluded from our study.

A potential risk of gastric acid suppression that has been described are infectious complications especially pneumonia and enteric infections including Clostridium difficile (C. difficile). Several retrospective reports and meta-analysis have found a slight increase in risk of community acquired pneumonia with use of H2-blocking acid suppressing agents including famotidine but not to the extent of that with the use proton pump inhibitors (PPIs).[41] However, a recent double blinded trial of over 17,000 patients only found a two-fold risk of C. difficile diarrhea amongst patients on long term acid suppression with proton pump inhibitors and no increased risk of pneumonia.[42] Famotidine does not lead to the profound and prolonged acid suppression seen with PPIs, and there is tachyphylaxis to repeated doses of famotidine starting on Day 1 when using a dose of 40mg/day. In summary, since there is tachyphylaxis to acid suppression with famotidine and the risk of pneumonia is lower than with PPIs,[43] which are readily available over the counter, and since we will be treating patients with mild to moderate symptoms of COVID-19, we believe the risk to benefit ratio to favor treatment of COVID-19 patients with famotidine to prevent development of COVID-19.

There are reports about possible drug-drug interactions between famotidine and tizanidine.[44] Therefore, patients enrolled in this study will be educated that they should not take tizanidine during the study period. The other concomitant medications recommended to be avoided will be Dasatinib, Delavirdine Mesylate, Cefditoren, and Fosamprenavir.

Although our group has not conducted detailed safety studies on famotidine at 240mg/day dosing, there are several published reports which indicate a favorable side effect profile. In a report from Howard et al, famotidine (MK-208, YM-11170) was used in eight patients with Zollinger-Ellison (ZE) syndrome causing gastric hypersecretion for up to nine months with mean daily dose of 0.24g/day. The only reported side effects in this study were mild leucopenia in three of the eight patients which was not attributed to the famotidine since upon further review it was present prior to initiation of famotidine. In a follow up larger study of 32 patients (age range 22-68) with ZE syndrome from the same study group, a mean dose of 240mg/day was used to achieve adequate acid suppression. The maximum allowable dose of

famotidine in this study was 0.8 grams/day. Despite, these higher doses of famotidine than those approved by the FDA, there were no hematological, biochemical, or clinical evidence of toxicity from famotidine in the 32 patients[45]. Although, these are both small studies (total n=40 patients), one can infer that famotidine at 240mg/day dosing is unlikely to cause serious adverse events. [46]

c. Drug Accountability

During virtual visits with the patients, we will count number of remaining pills with the patient using the two-way video conference capability of the electronic tablets. The study investigator will record this information for record keeping. All drug accountability records will be kept current and contain the dates, quantity, and study medication dispensed to each subject. The PI must be able to account for all opened and unopened study drug. All unused study drug must be disposed of at the site or returned to the sponsor or designee. All drug accountability records will be made available for inspection by regulatory agencies and kept on file onsite as per Northwell Health institutional policy.

d. Guidelines for Delay, Reduction and/or Discontinuation of Study Medications

Dose modification for an individual subject will not occur. Treatment will be discontinued for subjects experiencing severe Adverse Events determined to be likely or definitely related to the study drug.

e. Prior and Concomitant Medications

Concomitant use of immunosuppressive therapy and/or investigational study drugs for the treatment of COVID-19 are an exclusion criterion for participation as they may introduce bias. Any other treatment administered from the first dose of study drug to the final study assessment will be considered concomitant medication and recorded per subject.
Due to the resorption reducing effects of gastric acid suppression, we recommend participants to avoid concomitant use of dasatinib, delavirdine mesylate, cefditoren, and fosamprenavir.

f. Method of Assessing Treatment Compliance

Study drugs will be self-administered per protocol on Days 1-14. Medication records will be made available for inspection by the sponsor and/or regulatory agencies, and kept on file onsite as per Northwell Health institutional policy. Patients will be called by the study team on the telephone or through the HIPAA compliant VitalCare app to complete medication records, case report forms.

g. Subject Withdrawal/Discontinuation

A subject has the right to withdraw from the study at any time. The investigator and/or sponsor have the right to discontinue study medication if it is no longer in the best interest of the subject to continue. However, even though patients are no longer taking study medication, they will remain in the study and be included in the analysis. They will be regularly followed up with regards to safety and efficacy. The only reason for study withdrawal is if the patient withdraws consent or if patients are lost to follow up. If a subject withdraws from the study, they will keep the equipment as to decrease the spread of COVID.

i. Subject Replacement

Subjects that withdraw before the virtual visit on Day 0 (Baseline assessment) will be replaced as feasible, to reach the enrollment goal of 84 subjects. Patients will only be replaced if they withdraw from the study before randomization.

• STUDY PROCEDURES

The following section describes the study procedures divided in Screening, Enrollment and Treatment period. Appendix D "Approach" is a continuous text describing in detail what each step entails.

a. Screening

The research coordinator will be notified about potentially eligible patients who require screening. Screening will be done remotely by the study coordinators reviewing the results from the patients tested at the Northwell Laboratory and confirming eligibility with the investigator at Northwell Health.

b. Enrollment

The first step will be screening the patient for interest and eligibility to participate in the trial. The screening, consent and enrollment process will be performed via the telephone with a conference call involving two additional members of the research team to serve as witnesses to the informed consent. Participants will be called and if interested in participation, investigators will go through the screening questionnaire with them, prior to consent to confirm eligibility. When possible, an electronic software based consent process will be utilized. We plan on using REDCAP for electronic consenting, this electronic consent system is 21 CFR 11 compliant and we will follow published FDA guidance on electronic consenting. Briefly, this will involve emailing the consent to the patient, go over it together on the telephone and have the patient sign it electronically which will simultaneously generate signed copies for the study teams' and patients' personal records once also signed by the research time. The research coordinator will obtain contact information of the patient's close contacts in case of non-response during their enrollment. Upon meeting the inclusion/exclusion criteria (determined during screening call) including consent, the research coordinator will officially enroll the subject and implement the randomization procedure. Once consented and randomized, any virtually enrolled patients will have the study kits which includes the electronic tablet with pre-installed VitalCare app paired with peripheral devices and study medication couriered to their home address.

c. Treatment Period

Famotidine will be prescribed at 80 mg TID for a maximum of 14 days, or until hospital admission.
Subjects will receive study drug within one calendar day of undergoing enrollment. Using the HIPAA compliant VitalCare app, subjects will be asked to report medication intake, occurrence of possible adverse events, and perform O2 saturation, spirometry measurements, body weight and body temperature measurements and record the severity of their symptoms daily on the PROM questionnaire, see Appendix E, from Day 1 to Day 28 and on day 60. Participants will complete a daily questionnaire on the VitalCare App on the tablet computer. For patients that are unable to self-record responses electronically due to illness or other circumstances, they will be contacted by phone by the study team to record verbal

responses. The daily measurements of physiological data will be performed with equipment provided as part of the study (see section 10.5). The patient can integrate the acquired data (including body temperature, body weight, spirometry, and pulse oximetry) into the PROM questionnaire form by uploading it automatically by coupling the measurement devices to the tablet via Bluetooth, or verbally with a study staff member if unable to self-record responses electronically. In the evening, trained study personnel will review if each patient has performed the physiological measurements and filled out the PROM questionnaire. If the patient has not done so, study personnel will send reminders and or call the respective participant. Subjects will wear a Fitness tracker that continuously monitors movement and energy expenditure for the duration of the study. On Days 7, 14 and 28, the study subjects will undergo a virtual visit. These HIPAA compliant virtual visits will take place through the VitalCare app with a study investigator. LabFly, a remote phlebotomy service will be utilized for all research labs including blood draws and Nasal Swabs. They will visit the patient on Days 1,7,14,28. The blood tests on Day 14 and 28 will be optional. A serological test for Anti Sars-Cov 2 antibodies will be performed on Day 1 and Day 28. An additional Nasal Swab will be taken on Day 1 and stored until end of study for use of detection of specific viral variants using targeted sequencing approaches. This additional swab will be optional. On Day 60, there will be a final follow-up questionnaire including an assessment of adverse events, which will be completed by telephone (if patients have experienced complete symptom resolution by day 28). This questionnaire will be administered through the VitalCare app or via telephone if unable to complete through the app.

We will ascertain vital status in all randomized patients through the daily questionnaire. If we are unable to reach the participant after three attempts to contact within 24 hours, we will contact their emergency contact.

d. Follow-up

Subjects will be followed for 60 ±5 days. If a patient gets hospitalized, they will be followed up until discharge, which may be longer than 60 ±3 days. There should be very few cases of such patients.

We will follow up with patients that are pregnant during the course of famotidine treatment for up to 12 months post-EDD (estimated due date) at the following time-points: an interim timepoint between study enrollment and the estimated due date (EDD), EDD, 6 months post-EDD, and 12 months post-EDD. At these time points, maternal, fetal and neonatal adverse events will be assessed.

• EFFICACY ASSESSMENTS

See Section 2.

• EVALUATION AND REPORTING

a. Assessment of Safety Endpoints

Subject safety will be assessed continuously while in study. Subject safety will be assessed in the questionnaires on Days 1-28, at virtual visits on Days 0,7,14 and 28, and in a follow-up questionnaire on Day 60.

For breastfeeding women, safety of the breastfed infant will be assessed at these timepoints as well.

Safety of pregnant subjects, fetus and newborn will additionally be inquired at an interim timepoint between study enrollment and the estimated due date (EDD), EDD, 6 months post-EDD, and 12 months post-EDD. There, possible adverse events to mother, fetus and newborn, and outcome of pregnancy, including spontaneous or voluntary termination, stillbirth, details of the birth, and the presence or absence of major birth defects, or maternal and/or newborn complications will be inquired.

b. Adverse Events and Serious Adverse Events

i. Definition of Adverse Event (AE)

Adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

ii. Definition of Serious Adverse Event (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

iii. Classification of Adverse Event

1. Severity of Event

The following guidelines will be used to describe severity of Adverse Events (AE):

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

2. Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **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 intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge 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 after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge 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, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study 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.

3. Expectedness

The PI or other clinician responsible for determining causation of AEs will determine expectedness based on the known side effects and reactions listed in the drug monograph. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

iv. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded. Events will be followed for outcome information until resolution or stabilization.

For patients that are pregnant during the course of famotidine treatment, we will assess adverse events for mother, fetus and newborn for 12 months post-EDD.

For patients breastfeeding infants while on the study drug including 24h after the last dose, possible adverse events in the infant will also be assessed.

The PI of the study together with the clinical team and DSMB will review AEs and SAEs and will inform participants of the study of safety concerns, if indicated.

If a patient meets any of the following criteria, the treatment will immediately be discontinued:

- CrCl <60ml/min
- Evidence of skin rash that is moderate in severity or greater or suggestive of hypersensitivity reaction
- New onset elevation in liver associated tests, specifically an increase of at least 3 times the upper limit of normal for alanine transaminase levels or aspartate transaminase levels or any new onset elevation in bilirubin levels or any acute change in liver synthetic function as found by decrease in albumin level or elevation in prothrombin time. These patients will then be referred to a hepatologist for further evaluation and necessary care. Patients who have new onset elevation in liver function who do not meet these above criteria may continue in the trial but they will have their liver tests including alanine transaminase levels, bilirubin (including direct), albumin, prothrombin time rechecked in 24-48 hours and will be closely followed by a hepatologist during their participation in the trial.

For patients with new onset or documented worsening of baseline renal function, who require study drug discontinuation, an EKG will be performed to evaluate for potential QTc prolongation

v. Adverse Event Reporting

Adverse events (AE) will be documented immediately and reported to the PI or treating clinician for further evaluation as described above.

vi. Serious Adverse Event Reporting

Serious Adverse Events determined Possibly, Probably, or Definitely Related to the study intervention must be reported immediately to regulatory authorities and the DSMB.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event will be recorded.

The Principal Investigator (PI) will be responsible for notifying the Food and Drug Administration (FDA) via MedWatch of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after initial receipt of the information. These events will also be reported to the IRB.

vii. Reporting Events to Participants

Participants will not be informed of AEs and SAEs unless the AE or SAE happened to them.

viii. Events of Special Interest

N/A

c. Unanticipated Problems

i. Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

ii. Unanticipated Problem Reporting

The investigator or study team member who becomes aware will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Principal Investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported within 5 business days of the investigator becoming aware of the event.
- Any other UP will be reported within 5 business days of the investigator becoming aware of the problem.

d. Other Safety

i. Clinical Laboratory Evaluations

Blood samples and nasal swabs will be obtained at the patients home by LabFly using standard venipuncture and standard nasal swab procedure. Laboratory values will be obtained for white blood cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on Days 1 and 7, and optionally on day 14 and 28. The PI will be made aware of abnormal lab values. No more than 30 ml of blood will be drawn at each virtual visit.

ii. Vital Signs

Vital signs (Pulse, oxygen saturation, body temperature) will be collected daily with devices provided to the patients as part of the study and transmitted into the VitalCare App via Bluetooth. The devices are listed in section 10.5 and the data collection process is further described in section 10.2. There will be daily review of all patient's vital signs collected using the remote monitoring interface provided by Vital Tech (detailed in Appendix D). Briefly, a study investigator will review the vital signs collected daily and any alerts generated automatically by the software for vitals out of the normal range. The study investigator will call the patient and determine if these abnormal vital readings are not artefacts. When possible, repeat measurements will be obtained. If the subjects' condition is felt to be worsening, they will be advised to seek medical care at nearest emergency room.

• STATISTICAL METHODS

a. Primary endpoint

The primary endpoint is cumulative incidence of symptom resolution at day 28, which will be estimated using time from treatment start to symptom resolution. Time to symptom resolution will be-defined as the number of days after randomization to the first time that total COVID-19 symptom score from 17 symptoms is ≤3 and no symptom having a score >1 for two consecutive days. The symptoms will not be weighted in this analysis. This symptom tool has been developed based on experience from a prior case series of famotidine in patients with COVID and in concordance with the FDA guidelines. This tool has not yet been validated in a randomized clinical trial. For patients who have not achieved symptom resolution by day 28, their time to symptom resolution will be censored at day 28. If a patient has early withdrawal from the study before symptom resolution within 28 days, then his/her time to symptom

resolution will be censored at the day of withdrawal. Death without symptom resolution will be treated as a competing risk event. However, very few incidences of death are expected in our enrolled patients.

b. Sample size consideration

We are planning to enroll patients for 5 months and expected to enroll 84 patients with confirmed COVID-19 infection in total. Because of lack of preliminary data about the total symptom scores using all 17 symptoms and within each stratum by age and gender, we estimate our detection power under different assumptions as shown in the Table 2a below while ignoring the stratification factors. Table 2a suggests that if assuming the cumulative incidences of symptom resolution at day 28 in the treatment arm and placebo arm are 80% and 50%, respectively, then 84 patients will achieve 92.34% power to detect such difference using a two-sided log-rank test with type-I error controlled at 0.05. Because we expect very few deaths will occur by day 28 among the study participants, the drop in the study detection power is minimal because of competing risk events. However, even if we assume that the cumulative incidence of death at day 28 in each arm could be as high as 10% (that is, 5 death events happened in each arm by day 28 without symptom resolution), in the aforementioned example, the minimal detecting power will decrease from 92.34% to 88.78%.

Table 2a: Study power of detecting different cumulative incidence (CI) of symptom resolution at day 28 between two study arms under different assumed CI.[47] The type I error is set at 0.05 and study sample size is set at 50 in each arm. Two-sided log-rank test is used for calculation.

Cumulative Incidence of symptom resolution at day 28 in the placebo arm	Cumulative Incidence of symptom resolution at day 28 in the treatment arm			
	75%	80%	85%	90%
50%	78.02%	**92.34%**	**98.46%**	**99.87%**
60%	39.69%	65.26%	**87.02%**	**97.69%**
70%	9.22%	24.17%	51.59%	**82.24%**

c. Statistical Analysis Plan for Primary Hypothesis

In general, patient baseline characteristics will be summarized with appropriate descriptive statistics. All baseline demographics and clinical data will be summarized by treatment arm using frequencies, rates, means, medians, standard deviations and quartiles appropriate to the dataset. There will be no inferential comparison of treatment arms with respect to baseline and demographic clinical data; such comparisons will be descriptive only. Unless otherwise specified, all results will be considered significant if $p<0.05$**.** All data analysis will be performed using SAS 9.4 (SAS institute Inc., Cary, NC).

All model assumptions will be diagnosed and data transformation may be needed to make the model assumption met. All analysis will employ the intent-to-treat (ITT) principle and results will be reported according to CONSORT guideline. All randomized patients in the groups to which they are randomly

assigned, regardless of the intervention they actually receive and regardless of subsequent withdrawal from treatment or deviation from the protocol for any cause will be included in the final analysis.

Our primary hypothesis of this study is that patients in the famotidine arm will have earlier symptom resolution than those in the placebo arm within 28 days. Our primary estimand is the cumulative incidence of symptom resolution by day 28 where symptom resolution is defined an earlier achievement of a daily cumulative symptom score of =/<3 in the treatment arm. The statistical analysis for the primary estimand will be blinded to if the patients were enrolled and followed in person or virtually. Cumulative incidence curves of symptom resolution till day 28 will be estimated by treatment arm. Cumulative incidence rates of symptom resolution at day 28 will be estimated and reported with its 95% confidence interval. Comparison of cumulative incidences between the treatment arm and placebo arm will be carried out using stratified log-rank test with age and gender as stratification factors. Death before day 28 is expected to be very rare in our study population. However, if there is any death before day 28 without achieving symptom resolution first and hence should be viewed as competing risk events, then Gray's test will be used instead first and followed by a Fine-Gray's regression model adjusting for two stratification factors (age and gender).[48,49] We expect to get same conclusion even if using stratified log-rank test without treating death as a competing risk event as we expect there should be very few deaths even if there are any deaths before day 28.

For a well-executed randomized clinical trial, we expect that patients enrolled in both study arms are balanced in co-morbidities and any other unobserved characteristics or clinical information. However, to improve the precision of our inference, we will further use Cox's proportional hazard regression model (if no competing risk event exists) or Fine-Gray's regression model (if death as a competing risk events exists) to adjust for overall comorbidity, age and baseline severity when the number of patients with symptom resolution allows.[50]

Intercurrent Events: In the event of a patient either discontinuing treatment or stopped participation for whatever reason after randomization, they will be included in the final analysis. However, patients not participating prior to randomization will be replaced via further enrollment. Similar analysis will be carried out by using the *per protocol* (PP) data set which will include all ITT patients who did not have any relevant major protocol deviations and have taken at least 70% of prescribed Famotidine. The PP data will be used for sensitivity analysis of the primary efficacy endpoint. For the purposes of the PP definition, the use of REM on or prior to Day 28 will constitute a major protocol violation. Accordingly, data on subjects who receive REM on or prior to Day 28 will be excluded from the PP dataset. In addition, all symptom scores collected after patients got hospitalized will be set as missing in the PP data analysis as they would get other interventions once hospitalized.

d. Missing Data

The missing data pattern for longitudinal studies is typically complicated. In our study, we will send reminders and ultimately make phone calls to study participates that did not yet fill out the PROM questionnaire in order to minimize missing data. Also, all site investigators will be trained about the importance of retention and steps to prevent missing data. Missing data in our study is highly like to be intermittently missing pattern and few deaths are expected. Therefore, missing at random is high likely to be the missing data mechanism in our study. As a sensitivity analysis, we will also use multiple imputations by chained equation to impute missing symptom scores,[51,52] use complete cases only for analysis and pattern mixture approach[53,54]which is useful in the case of informative dropout.

e. Statistical Analysis Plan for Secondary Objectives

There are ten planned secondary endpoints: *rate of symptom resolution over 28 days, cumulative incidence of symptom resolution at day 60*; *the relative change in the COVID-19 symptom score from baseline (Day 0 before taking any medication) to Day 7; clinical status ordinal score; Serious Adverse Events; Ferritin level on Day 7; Peripheral oxygen saturation on Day 7; Cumulative incidence of resolution (symptom score -decrease to <=1) of each individual symptom that are >1 at baseline listed in the extended COVID-19 symptom score; 28-Day Mortality; Proportions of patients having been hospitalized by Day 28*. The comparison between all longitudinal measurements such as clinical status ordinal scores, ferritin level and peripheral oxygen saturation will be first illustrated using spaghetti plots. We will also use stacked bar charts comparing the distribution of the ordinal scale of symptom scores for the both arms longitudinally for illustration purpose. No multiple testing adjustment is planned for secondary data analysis.

Rate of symptom resolution over 28 days: The rate of symptom resolution will be assessed using all available absolute symptom scores (the sum of scores over all individual symptoms) for all patients with intention to treat from day 0 to day 28 using a mixed random effect model assuming a linear change over time for ln(score+1).

Cumulative Incidence of symptom resolution at day 60: For this efficacy endpoint, the follow-up time period for each patient will be extended to be 60 days. Time to symptom resolution here is very similar to our primary efficacy endpoint. It is defined as days from randomization to the first-time achieving symptom resolution, death or last follow-up up to day 60 whichever occurs first. Death will be viewed as a competing risk event here, but again we expect very few deaths by day 60. The analysis for this endpoint will be similar to how we analyze our primary endpoint and will be carried out using both ITT analysis and PP analysis.

Relative change in symptom sore on Day 7 compared to baseline: The relative change in the COVID-19 symptom score from baseline (Day 0 before taking any medication) to Day 7, defined as the difference of Day 7 total symptom score and baseline symptom score over 6 symptoms (Day 0 total symptom score) divided by baseline symptom score will be assessed. The hypothesis here is that patients on the treatment arm will have a significantly bigger change/drop in the total symptom score than patients on the placebo arm. Since the data are longitudinal and have hierarchical structure, we will use a linear mixed effects model for the analysis. The fixed effects of the model will include group (treatment and placebo), visit (Day 0-28) and an interaction between group and visit. The baseline total symptom score will be used as covariate. Due to the lack of preliminary information by age and gender, these stratification factors were not used in the sample size calculation. However, these two stratification factors will be adjusted for in the linear mixed model. This model will include a random intercept at the patient level to account for correlations due to the repeated measurements from the same patients. The dependence structure for longitudinal data from the same patient will be selected with the Akaike Information Criterion with the priority order: unstructured > autoregressive with order 1 (AR(1)) > Toeplitz > compound symmetry > independent. More specifically, the model will take the following mathematical form,

$$Y_{it} = \alpha_t + \beta_t X_i + \gamma_i Z_i + b_i + e_{it} \qquad (A1)$$

Where Y_{it} is the percent change of total symptom score for subject =1,…, n at Day t; X_i is a binary indicator for treatment (1 for subjects in the treatment arm and 0 otherwise), Z_i stand for covariates including baseline symptom score, gender, age; $\alpha_t, \beta_t, \gamma_i$ are unknown coefficients; $b_i \sim N(0, \sigma_b^2)$ is a Gaussian random effect to reflect the correlation of total symptom score from the same subject and the residual vector $e_{it} \sim MVN(0, \Sigma_e)$. The form of Σ_e will be selected with the Akaike Information Criterion (AIC). The regression coefficients should satisfy appropriate constraints for model identifiability. Under this model, β_7 represents the symptom score reduction at Day 7 in the treatment arm compared to placebo group. Testing the hypothesis $H_0: \beta_7 = 0$ will provide the secondary data analysis results. This model (A1) allows for estimating the symptom score changes at different time point within each arm and their differences at any time point. This model also allows us to later adjust for other possible confounding factors such as patients' comorbidity. Model assumption such as normality will be diagnosed and data transformation may be applied if needed.

In analyzing this secondary endpoint, we will do both ITT and PP analysis.

Clinical progression status: Clinical status ordinal scores will be measured on a 7 point ordinal scale as shown in section 2.3.2. As the expected death or hospitalization is expected to be rare (<5%) in our study population, we will compare the proportion of patients who had clinical progression (defined as ever having an increase in the clinical status ordinal score by day 14) between two study arms. Estimated clinical progression rates and corresponding 95% Casella-Blyth-Still confidence intervals will be reported within each arm. Fisher's exact test will be used for the comparison. Because death and hospitalization are rare, our study may not have enough power to detect such difference. In addition to that, we will provide stacked bar charts comparing the distribution of the ordinal scores for the both arms at multiple time points.

Serious adverse events (SAE): For each specific type of SAE in addition to overall SAE, the estimated event rates and corresponding 95% Casella-Blyth-Still confidence intervals will be reported within each arm. Discontinuation or temporary interruption of famotidine use (for any reason) in the treatment arm will be described.

Levels of inflammatory markers: CRP, procalcitonin, and ferritin levels will be measured on Days 1, 7, and optionally on day 14 and 28. We hypothesize that patients in the treatment arm will have a significantly lower levels than those in the placebo arm. For example, based on literature on ferritin we assume mean and SD at day 1 and day 7 for placebo arm of 600ng/ml +/- 100 ng/ml and mean and SD on day 7 for treatment arm of 400ng/ml +/- 100 ng/ml, 50 patients per arm will have more than 90% power using a two-sided two-sample t-test with alpha 0.05 (PASS 12). We will further use a linear mixed model for longitudinal data to further compare ferritin levels between two arms on Day 7 in addition to other optional time points (Day 14 and 28). Such comparison will be performed as both ITT analysis and PP analysis. Age, gender and study sites will be used as covariates. CRP and procalcitonin will be analyzed in a similar way. No multiple testing adjustment for comparing these three markers is planned as these are our secondary endpoints.

Peripheral Oxygen Saturation Peripheral oxygen saturation will be measured daily from Day 1 to Day 28. Days with oxygen saturation ≤ 98% before reaching over 98% for patients within each arm will be

first described using appropriate statistics such as mean and SD. We expect that the placebo group would not have any increase by Day 7 but the treatment group would have an increase of 4-6% from 90-94% to 96-98% within 7 days. Assuming a conservative SD being 2%, 50 patients per arm will have more than 90% power to detect such difference on Day 7 using a two-sided two-sample t-test with alpha 0.05 (PASS 12). Analysis for peripheral oxygen saturation on Days 7 will be compared using similar analysis methods for comparing ferritin levels.

Individual symptom resolution: Cumulative incidence of resolution (symptom score decrease to <=1) of each individual symptom that are >1 at baseline listed in the extended COVID-19 symptom score will be estimated. Time to individual symptom resolution is defined as days from randomization to the time achieving symptom resolution, death or last follow-up up to day 60 whichever occurs first. Death will be viewed as a competing risk event here, but we expect very few deaths by day 60. Analysis for these time to individual symptom resolution will be very similar to how we analyze for the primary end point and will be carried out both as an ITT analysis and a PP analysis.

28-Day Mortality: Mortality rates by day 28 within each study arm will be estimated using the proportion of death occurred by day 28 and reported along with 95% Blyth-Casella-Still confidence intervals. The comparison of 28-day mortality between two arms will be carried using Fisher's exact test because we expect very few deaths by day 28.

28-Day Hospitalization*:* Proportions of patients having been hospitalized by Day 28 will be used to estimate 28-day hospitalization rates. Corresponding 95% Blyth-Casella-Still confidence intervals for 28-day hospitalization rates will also be reported. The comparison of 28-day hospitalization will be carried using Fisher's exact test if hospitalization is a rare event or by a conditional logistic regression model after adjusting for our stratification factors - age and gender if # of hospitalization is larger than 10 patients.[55]

f. Statistical Analysis Plan for Exploratory Objectives

All longitudinal continuous measurements such as peak flow rates, all lab test results, body weight, body temperature, symptom scores for other symptoms, drop in the PCR copy numbers, activity measurements from all participants will be first illustrated using spaghetti plots within each arm. Linear mixed models for longitudinal measurements will be performed to explore the difference between two study arms after adjusting for stratification factors (age, gender and site). Model assumptions will be diagnosed and dependence structure will be selected using AIC. Such model will use all available data and provide estimated differences between any two time points or between two arms at each specific time point. Because of the exploratory nature of these analysis, multiple testing adjustment is not planned (20). However, for the comparison of all lab test results, we are planning to use false discovery rate at 10% to find candidates for further investigation. Antibody presence/positive rate at Day 28, and hospitalization rate will be estimated within each arm and reported with corresponding 95% Casella-Blyth-Still confidence intervals. Fisher's exact test will be used to explore the possible difference between two study arms. For patients who get hospitalized, their LOS as measured as days from admission to discharge will be reported with descriptive statistics such as median and interquartile range by study arm. We will also explore the correlation between virologic response as measured by the drop in the PCR copy numbers over time and other longitudinal measures such as symptom scores, ferritin levels through linear mixed models and explore if there is a cutoff value in the drop rate of PCR copy number that could be used to predict positive treatment response or disease recovery.

g. Safety Analysis

Safety population: The safety population includes all randomized patients who received at least one dose of the study drug. Analysis of the safety population will be done according to the treatment received (as treated).

h. Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will actively monitor interim data to review the ongoing safety of patients and can make recommendations about early study closure or changes to the protocol. The DSMB members will include and be led by independent and fully qualified physicians. The DSMB will convene once per month with additional meetings or conference calls scheduled as needed. The detailed operation of the DSMB is governed by a charter (see Appendix C.) describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for reporting.

• DATA INTEGRITY AND QUALITY ASSURANCE

a. Monitoring

The PI will monitor for quality assurance throughout the study duration to ensure safety and adherence to study protocols. Study-related monitoring may also be done by internal and external regulatory agencies, including the IRB. Study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

b. Data Collection

Subjects enrolled in this study will undergo laboratory testing as per protocol. The results of these tests will be collected, as indicated. On days 1-28 and on day 60, the patients are asked to fill out the study questionnaire (see Appendix E) that includes the “extended COVID-19 symptom score”, questions about medication use and adverse events, and the physiological measurements. This questionnaire is incorporated into the VitalCare App (see Appendix F). The patients will be provided clear instructions on how to score the severity of their symptoms and perform the daily physiological measurements. The data of these measurements can automatically be uploaded into the VitalCare software via Bluetooth. The fitness tracker will automatically send the acquired data into the VitalCare App via Bluetooth. Alternatively, the data can be retrieved at the final visit on Day 28. Timely collection of daily data through the electronic tablets will be assessed remotely by a study investigator through the web based VitalCare app’s administrator interface. In case of tablet malfunction, the patient will be contacted by phone by the study team to record verbal responses.

c. Data Management

A data management plan specifying all relevant aspects of data processing for the study will be maintained with the regulatory documentation for this protocol. All data coding (SAEs, baseline findings, medication, medical history, etc.) will be done using internationally recognized and accepted abbreviations. Northwell Health has designed and implemented a HIPAA compliant COVID-19 Datamart data collection tool which will be utilized to obtain clinical data for COVID-19 patients within the health system in addition to the medical record. The data for this clinical trial will be collected in RedCap.
The data collected on the VitalTech platform will not be kept by VitalTech and not used by them or third parties for other purposes. VitalTech will only serve as a data warehouse as per their internal guidelines. VitalTech will not claim 'ownership' of the stored data. The stored data will not be used by VitalTech. It will only be accessible to validated users (study investigators) through a password protected system with two factor identification.

d. Electronic Systems

Electronic systems that may be used to process data in this study will include:

- Biostatistics Randomization Management System (BRMS) ‑randomization
- RedCap – data collection CRF
- Statistical Analysis System (SAS) ‑ statistical review and analysis
- VitalTech platform

Data of patient recorded physiological measurements and PROM questionnaires will be collected on iOS based tablets using HIPAA compliant VitalCare by VitalTech. The tablet computer will be provided to the participants for participating in the study. VitalCare is a comprehensive cloud-based platform that aggregates, contextualizes, and delivers actionable data. An example of the interface the patients of this study will interact with is attached to this protocol (See Appendix F).

The data will be gathered via FDA-approved Bluetooth compatible devices: Jumper Pulse Oximeter, Jumper thermometer, MIR spirobank II spirometer, and Taiza weight scale. In the event that patients do not have internet access, a tablet with a Monthly 4G-LTE Data Plan will be provided for the duration of the study.

Patients will be able to keep all devices provided to them after study completion including the iPad, Jumper Pulse Oximeter, Jumper thermometer, MIR spirobank II spirometer, and Taiza weight scale.

e. Equipment for patient acquired Data

In order to fill out the PROM questionnaire including the daily physiological measurements, each patient will be handed a set of equipment and software free of charge at day 1. This includes an iPad tablet computer and all measurement devices for physiological monitoring. The equipment for the physiological measurements (Spirometer, thermometer, pulse oximeter) are to be connected to the tablet device via Bluetooth for ease of usage. This VitalCare platform is tested and suitable for people with limited technological understanding.

The set of equipment and software will include the following:

- 1 iOS based tablet computer (iPad) including:
    - Pre-installed VitaCare App as a platform to fill out the PROM questionnaire and collect physiological measurements. The App includes the PROM questionnaires, consent form, instructions on how to fill out the questionnaire and information material including but not restricted to a list of possible adverse events.
    - Monthly 4G-LTE Data Plan in case the patient does not have other internet connection
- 1 Bluetooth compatible Pulse Oximeter (Jumper 500F – D307074; 510(K):K170965) with instructions on its use
- 1 Bluetooth compatible Weight scale (Taiza TGF) with instructions on its use
- 1 Bluetooth compatible Thermometer (Jumper FR400 – D318254; 510(K): K172795) with instructions on its use
- 1 Bluetooth compatible Spirometer (MIR Spirobank II: 510(K): K061712) with instructions on its use
- 1 Bluetooth compatible Fitness Tracker (VitaBand Wearable Activity Tracker with charger)
- 1 Paper copy of PROM questionnaires, consent form, instructions on how to fill out the questionnaire and information material including but not restricted to a list of possible adverse events.

The Data sheet for the equipment is appended to the protocol (see Appendix G).

What will happen to the study kits after completion of study?

Since it will be difficult to properly disinfect the study kit including the tablet and peripheral devices, the subjects will be allowed to keep the study kits after the duration of the study. The purchase price for one study kit is $957.50. We will inform study participants to not share the kit with anyone as this can be a potential vector of infection. These measures will minimize the risk of spread of the virus. No further data collection will occur after the end of the study period. The subjects will be educated that the devices do not serve any medical purpose after the study ends. At the end of their participation, each subject will be off-boarded from the study through the VitalCare remote app, which will stop all data collection and connection to the devices.

f. Study Documentation

i. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded electronically. All required CRFs must be completed for every study subject. The PI will ensure the accuracy, completeness, and timeliness of the data and will provide his electronic signature upon review.

Copies of paper CRFs will be retained as part of the study record and available for inspection by regulatory authorities. The electronic systems used for data management all employ an audit trail that will reflect any changes made to study records.

ii. Record Retention and Storage

All essential study documents, including ICFs, source documents, CRFs, drug accountability records, and regulatory documentation will be stored in a locked office at the:

Office of Clinical Research

1981 Marcus Avenue

Suite E 110

Lake success NY 11042

After the study is completed, binders will be kept in long term storage with Iron Mountain. All documents will be retained for at least 15 years following the completion or discontinuation of the study.

g. Operational Procedures

A 'Meta-Site' will be established to coordinate study personnel working remotely to perform study tasks that do not need to be completed on-site. These will include but are not limited to the following: 1) track all data, 2) coordinate meetings, 3) maintain regulatory documentation, 4) oversee study personnel and address staffing needs. A Meta-Site Principal Investigator will be identified to oversee this team.

• PUBLICATION POLICY

a. Publication and Public Disclosure of Clinical Trial Information

This study and results will be made publicly available on ClinicalTrials.gov. Processes for publications resulting from this study will be outlined separately.

• ETHICS AND ADMINISTRATIVE INFORMATION

a. Good Clinical Practice Statement

It is the responsibility of the PI and all study personnel to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

b. Confidentiality

All appropriate measures will be taken to ensure that the anonymity of each subject is maintained. Subjects will be identified by an alphanumeric code only on CRFs and other related documentation. Source documentation that may not be coded will be kept confidential. Vitaltech does not store any PHI on the tablet. Everything is communicated through the app to the cloud server via the internet. The device utilized is 21 CFR Part 11 compliant.

c. Informed Consent

It is the responsibility of the PI or other IRB-approved study personnel to obtain
informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the potential subject in language that he/she can understand.

Waiver of HIPAA authorization to determine patient eligibility for study and to perform screening questionnaire

Since we will have to access patient records and approach patients identified to have tested positive for the virus remotely through a telephone call, we request a waiver of HIPAA authorization for two steps. In the first step, we will use information provided to Northwell Health by the patients such as their telephone number, primary care provider only for the purposes of determining their eligibility for the study. Once determined to be eligible, in the second step, we will call the patients to explain how we came about their information, determine interest and apply the screening questionnaire. Without a waiver we cannot conduct this study. as this is the best way to contact the patients for their consideration of participation and it is not reasonable to consent patients if they are not eligible. We will store the requested information for determining eligibility and the screening questionnaires in a secure manner and this data will be discarded if patients are not determined to be eligible/screened out and not enrolled into the study.

We request a waiver of documented consent for going through the symptom questionnaire. The symptom questionnaire will be used to confirm eligibility We do not want to waste a person's time consenting them for the study if s/he is not eligible. The symptom questionnaire is a minimal risk intervention and does not require written consent outside the research context.

This following guidance is based on FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic involving patients in isolation where direct access is not feasible due to infection control measures and will be used or adapted to obtain consent as the situation requires.

- When possible, consent and HIPAA Authorization should be obtained using an electronic method (i.e. e-consent via iPad or computer).
- When informed consent and HIPAA Authorization cannot be obtained electronically, investigators should do the following:

1. The investigator obtaining consent virtually through a three-way phone call or video conference with (a) the patient, (b) a witness, and (c) if desired by the patient, additional participants (e.g., next of kin)

A. The consent process must include the following steps:

- Each attendee on the call or video conference identifies him/herself (include name and role/relationship to patient)
- Investigator reviews the consent form with the patient and answers any questions that occur during the conversation.
- Witness verbally confirms that patient's questions have been answered. If the healthcare worker in the room serves as the witness, the healthcare worker must sign the consent form as witness to the consent process.
- Investigator asks the patient to confirm that the patient is willing to participate in the trial and to sign the consent document while the witness is present or listening on the phone or video conference.
- Patient verbally confirms that s/he would like to participate in the trial and patient signs and dates the consent form.

- The Investigator and witness should sign and date a copy the consent form and provide individual attestation that the patient agreed to participate in the study and signed the informed consent form. (See COVID-19 Witness Attestation form & COVID-19 Investigator Attestation form)

OR

1 Witness – It is preferred for the witness to be impartial (not associated with the study team) when possible.

B. The enrollment note must include the following:

- Details of the consent process (see COVID-19 Enrollment note)
- If applicable, a description of why the signed consent document was not retained (e.g., due to contamination)

d. Regulatory Compliance

The Northwell Health Institutional Review Board (IRB), as described in ICH guidelines for GCP, will provide regulatory oversight of this clinical study. The IRB will review and approve:

- The protocol, Informed Consent Form, and advertising materials,
- Amendments or modifications to the protocol or ICF before implementation,

In addition, the IRB will be informed of any event likely to affect the safety of patients or the conduct of the study. Records of the IRB review and approval of all study documents will be kept on file by the PI.

e. Protocol Deviations

Major and minor protocol deviations will be reported according to institutional policy. Any abnormal values seen on the vitaltech system, confirmed by a physician to not be of clinical relevance will not be escalated and do not constitute deviations.

f. New Information Affecting the Conduct of the Study

If new information affecting either the conduct of the study or the initial risk/benefit assessment becomes available, this protocol will be amended as needed and submitted for IRB review. Subjects will be informed and required to provide informed consent.

g. Protocol Amendments

All amendments or modifications to this protocol will be reviewed and approved by the IRB prior to implementation. In the event that a modification is required in an emergency situation, the IRB will be notified immediately.

h. Study Termination

The sponsor, investigator, and/or regulatory agencies have the right to terminate the study prematurely on the basis of safety, efficacy or futility.

- **REFERENCES**

1. To, K. K.-W. *et al.* Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect. Dis.* **20**, 565–574 (2020).
2. Wu, Z. & McGoogan, J. M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA* **323**, 1239 (2020).
3. Catanzaro, M. *et al.* Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. *Signal Transduct. Target. Ther.* **5**, 84 (2020).
4. Wang, Y. *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* **395**, 1569–1578 (2020).
5. Geleris, J. *et al.* Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* NEJMoa2012410 (2020) doi:10.1056/NEJMoa2012410.
6. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N. Engl. J. Med.* NEJMoa2021436 (2020) doi:10.1056/NEJMoa2021436.
7. NIH. Therapeutic Management of Patients with COVID-19 . Available from: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/.
8. Tenforde, M. *et al.* Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. *MMWR Morb Mortal Wkly Rep* 993–998 (2020) doi:http://dx.doi.org/10.15585/mmwr.mm6930e1external icon.
9. Food and Drug Agency Information Sheet on Famotidine, Reference ID: 4280861. 1986. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019462s039lbl.pdf.
10. Wu, C. *et al.* Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm. Sin. B* **10**, 766–788 (2020).
11. Loffredo, M. *et al.* The Effect of Famotidine on SARS-CoV-2 Proteases and Virus Replication. *Prepr. bioRXiv doi https//doi.org/10.1101/2020.07.15.203059*.
12. Freedberg, D. E. *et al.* Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study. *Gastroenterology* (2020) doi:10.1053/j.gastro.2020.05.053.
13. Mather, J., Seip, R. & McKay, R. Impact of Famotidine Use on Clinical Outcomes of Hospitalized COVID-19 Patients. *Am. J. Gastroenterol.* (2020).
14. Janowitz, T. *et al.* Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. *Gut* gutjnl-2020-321852 (2020) doi:10.1136/gutjnl-2020-321852.

15. Harris P. All of Us Research Program Covid-19 Participant Experience (COPE) Survey (PPI). 2020. https://www.phenxtoolkit.org/toolkit_content/PDF/NIH_COPE.pdf.
16. Drew, D. A. *et al.* Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science (80-.).* **368**, 1362–1367 (2020).
17. Richardson, S. *et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* **323**, 2052 (2020).
18. El Miedany, Y., El Gaafary, M., Youssef, S. S. & Palmer, D. Incorporating patient reported outcome measures in clinical practice: development and validation of a questionnaire for inflammatory arthritis. *Clin. Exp. Rheumatol.* **28**, 734–44.
19. Schroeder, K. W., Tremaine, W. J. & Ilstrup, D. M. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. *N. Engl. J. Med.* **317**, 1625–1629 (1987).
20. Oken, M. M. *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am. J. Clin. Oncol.* **5**, 649–55 (1982).
21. *Food and Drug Administration (2020) 'COVID-19: Developing Drugs and Biological Products for Treatment or Prevention. Guidance for Industry.'*
22. O'Keefe, J. B. et al. Predictors of disease duration and symptom course of outpatients with acute covid-19: a retrospective cohort study. *Prepr. MedrXiv doihttps//doi.org/10.1101/2020.06.05.20123471* (2020).
23. Food and Drug Administration. Assessing COVID-19- Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. (2020).
24. Lippi, G. & Plebani, M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin. Chem. Lab. Med.* **58**, 1131–1134 (2020).
25. Wang, F. *et al.* The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI insight* **5**, (2020).
26. Tian, J. *et al.* Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. *Lancet Oncol.* **21**, 893–903 (2020).
27. Wölfel, R. *et al.* Virological assessment of hospitalized patients with COVID-2019. *Nature* **581**, 465–469 (2020).
28. Cohen, P. & Blau, J. Coronavirus disease 2019 (COVID-19): Outpatient evaluation and management in adults. *UpToDate* https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-outpatient-evaluation-and-management-in-adults#H197435016 (2020).
29. Baker, J. G. A study of antagonist affinities for the human histamine H2 receptor. *Br. J. Pharmacol.* **153**, 1011–21 (2008).
30. Staiger, C., Simon, B. & Kather, J. X. *Comparative effects of famotidine and cimetidine on antipyrine kinetics in healthy volunteers. Br J. clin. Pharmnac* (1984) doi:10.1111/j.1365-2125.1984.tb05031.x.
31. Echizen, H. & Ishizaki, T. Clinical pharmacokinetics of famotidine. *Clin. Pharmacokinet.* **21**, 178–94 (1991).
32. Takabatake, T. *et al.* Pharmacokinetics of famotidine, a new H2-receptor antagonist, in relation to renal function. *Eur. J. Clin. Pharmacol.* **28**, 327–331 (1985).
33. Spinner, C. D. *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. *JAMA* **324**, 1048 (2020).
34. Lenze, E. J. *et al.* Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19. *JAMA* (2020) doi:10.1001/jama.2020.22760.

35. World Health Organization. *WHO R&D Blueprint. novel Coronavirus. COVID-19 Therapeutic Trial Synopsis*. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf (2020).
36. Biswas, S., Benedict, S. H., Lynch, S. G. & LeVine, S. M. Potential immunological consequences of pharmacological suppression of gastric acid production in patients with multiple sclerosis. *BMC Med.* **10**, 57 (2012).
37. Matok, I. *et al.* The Safety of H 2 -Blockers Use During Pregnancy. *J. Clin. Pharmacol.* **50**, 81–87 (2010).
38. Food and Drug Administration. *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials. Guidance for Industry*.
39. Famotidine - Drugs and Lactation Database (LactMed) - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK501267/.
40. Powell, J. J., Jugdaohsingh, R. & Thompson, R. P. H. The regulation of mineral absorption in the gastrointestinal tract. *Proc. Nutr. Soc.* **58**, 147–153 (1999).
41. Eom, C.-S. *et al.* Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *Can. Med. Assoc. J.* **183**, 310–319 (2011).
42. Moayyedi, P. *et al.* Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. *Gastroenterology* **157**, 682-691.e2 (2019).
43. McRorie, J. W., Kirby, J. A. & Miner, P. B. Histamine 2 -receptor antagonists: Rapid development of tachyphylaxis with repeat dosing. *World J. Gastrointest. Pharmacol. Ther.* **5**, 57 (2014).
44. Poudel, R. & Kafle, N. Tizanidine-induced acute severe cystitis in a female taking famotidine. *Clin. Pharmacol. Adv. Appl.* 83 (2015) doi:10.2147/CPAA.S86933.
45. Howard, J. M. *et al.* Famotidine: effective treatment of Zollinger-Ellison syndrome. *J. Clin. Gastroenterol.* **9 Suppl 2**, 23–5 (1987).
46. Howard, J. M. *et al.* Famotidine, a New, Potent, Long-Acting Histamine H2-Receptor Antagonist: Comparison With Cimetidine and Ranitidine in the Treatment of Zollinger-Ellison Syndrome. *Gastroenterology* **88**, 1026–1033 (1985).
47. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.
48. Gray, R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *J Am Stat Assoc* 1141–1154 (1988).
49. Fine, J. & Gray, R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 496–509 (1999).
50. Peduzzi, P., Concato, J., Feinstein, A. & Holford, T. Importance of events per independent variable in proportional hazards regression analysis: II. Accuracy and precision of regression estimates. *J. Clin. Epidemiol.* **48**, 1503–1510 (1995).
51. van Buuren, S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat. Methods Med. Res.* **16**, 219–242 (2007).
52. White, I. R., Royston, P. & Wood, A. M. Multiple imputation using chained equations: Issues and guidance for practice. *Stat. Med.* **30**, 377–399 (2011).
53. Little R. Modeling the drop-out mechanism in repeated-measures studies. JASA.1995; 90:1112-21.
54. Little R. Pattern-mixture models for multivariate incomplete data. JASA. 1995; 88:125-34.
55. Babyak, M. A. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic medicine*, *66*(3), 411-421 (2004)..
56. Taft, T. H. *et al.* Evaluating the reliability and construct validity of the Eckardt symptom score as

a measure of achalasia severity. *Neurogastroenterol. Motil.* **30**, e13287 (2018).

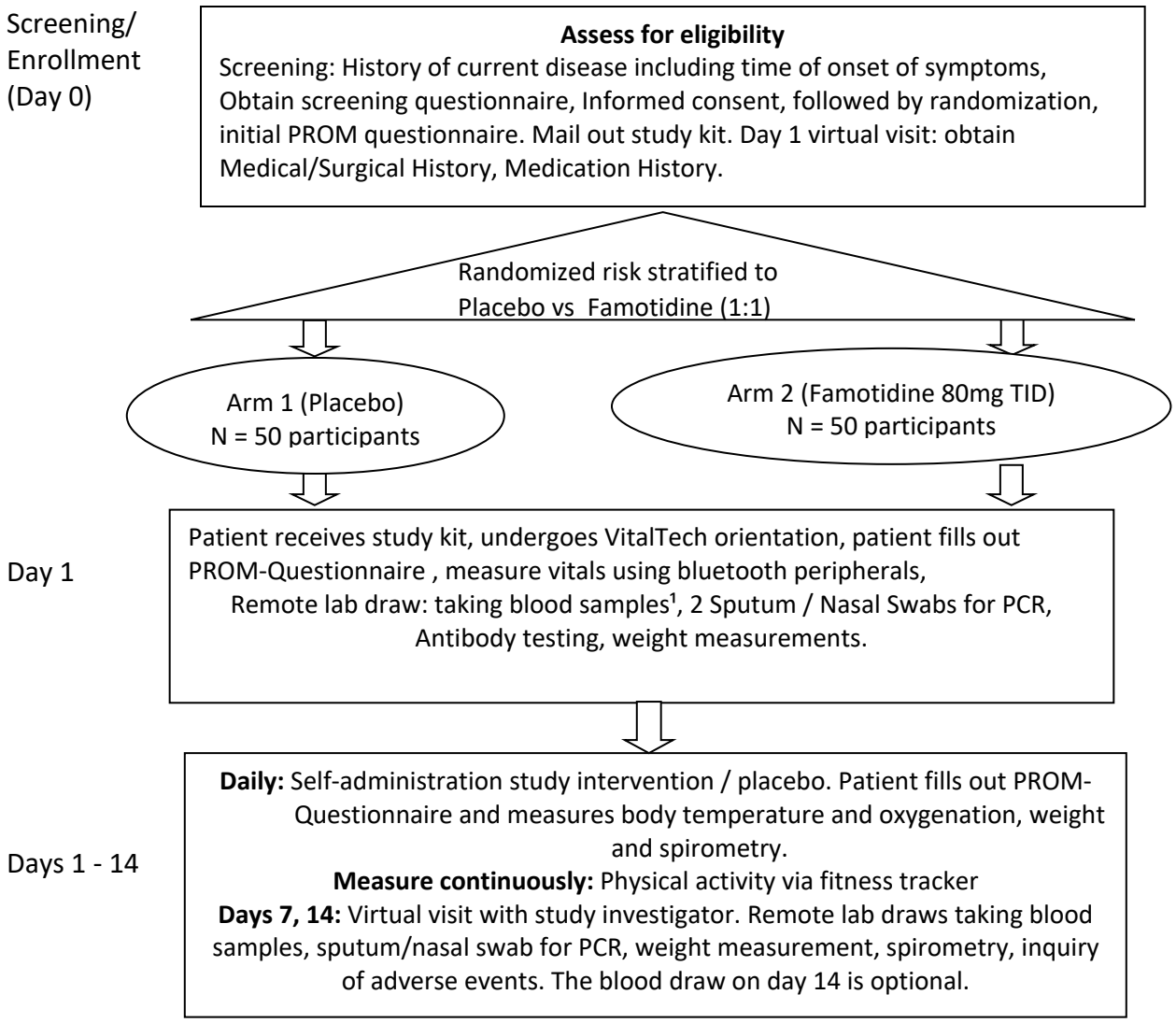
APPENDICES

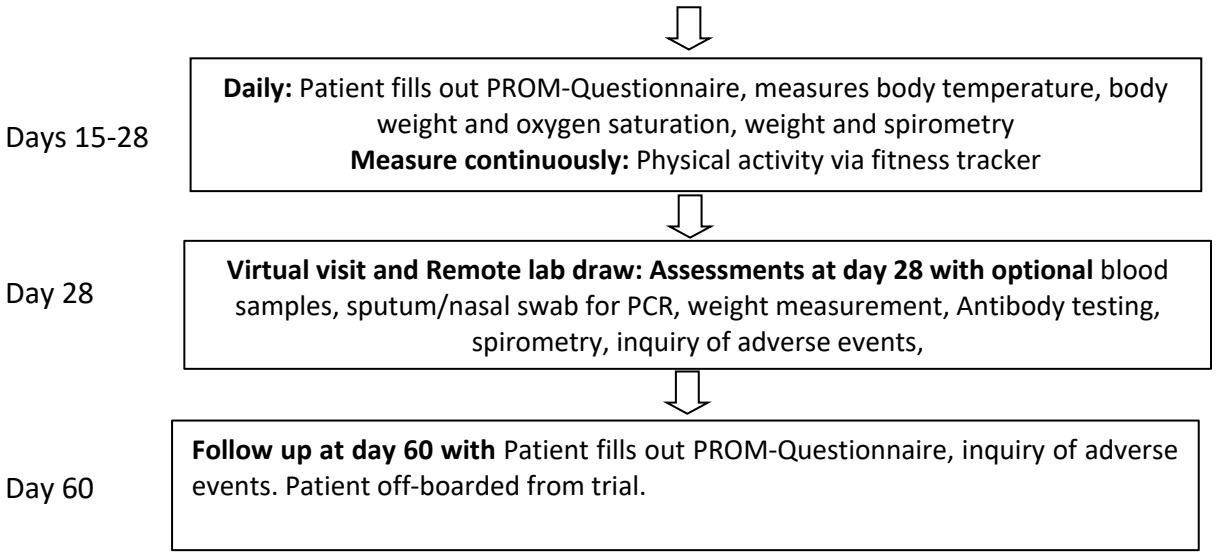
Appendix A: Schedule of Events

Procedures	Screening/Baseline/ Enrollment	Study Visit Day 1	Study Days: 1—14	Visits days 7 (+/- 2), 14 (+/- 2), 28 (+/- 4) (Virtual) Remote blood tests and swabs optional day 14 (+/- 2) and 28 (+/- 4)	Study days 0 - 28	Day 60 (+/- 5)	Unscheduled/ AE Assessment
Assess for eligibility	X						
Screening questionnaire	X						
Informed Consent	X						
Demographics	X						
History of Present Illness	X						
Medical/Surgical History	X						
Medication History (Outpatient and Inpatient)	X			X			
Creatinine Measurement		X					
Randomization	X						
Deliver drug		X					
Height	X						
Nasal Swab for PCR		X		X			
Nasal Swab for viral variant (Optional)		X					
Antibody testing		X		X			
Weight		X		X	X		
PROM Questionnaire					X	X	
Temperature Measurement		X		X	X		
Oxygen Saturation Measurement		X		X	X		
Vital Signs		X		X			
Physical Activity Monitoring					X		
Self-administration Study Intervention			X				
Hematological markers		X		X			
Serum Chemistry		X		X			

Inflammatory Markers		X		X			
Chemokine Panel		X		X			
Cytokine Panel		X		X			
D-Dimer levels		X		X			
Plasma Famotidine levels		X		X			
Adverse Event Review and Evaluation		X			X	X	
Complete Case Report Forms (CRFs)	X	X		X		X	
EKG							X

Appendix B Flow Diagram





[1] tests specified in Appendix A and Exploratory Endpoints (*Section 2.3.3*.).

Appendix C: Data Safety and Monitoring Board (DSMB) Charter

i. Introduction

A Randomized, Double-Blind, Comparative Trial of the Safety and Efficacy of Famotidine vs Placebo for the Treatment of Non-Hospitalized symptomatic Adults with COVID-19

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

ii. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

THE DSMB IS AN INDEPENDENT ADVISORY GROUP, AND IS REQUIRED TO PROVIDE RECOMMENDATIONS ABOUT STARTING, CONTINUING, AND STOPPING THE STUDY. IN ADDITION, THE DSMB IS ASKED TO MAKE RECOMMENDATIONS, AS APPROPRIATE, ABOUT:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety, and

- Notification of and referral for abnormal findings

The DSMB will make recommendations to the PI and if required to the FDA concerning continuation, termination and other modifications of the trial based on the observed beneficial or adverse effects of the treatment.

The DSMB may recommend pre-planned modifications based on comparative efficacy data. However, when trial data are examined in a comparative interim analysis, data analyses that were not prospectively planned as the basis for adaptations may unexpectedly appear to indicate that some specific design change (e.g., restricting analyses to some population subset, adjusting sample size, modifying the primary endpoint, or changing analysis methods) is ethically important or might increase the potential for a statistically significant final trial result. Unplanned modifications based on non-prospectively planned analyses can create difficulty in controlling the Type 1 error probability and interpreting the trial results.

In order to maintain study integrity, all systems will be protected. Anti-virus protection will be updated on every computer and a firewall will be used as the systems are connected to the Internet. In order to protect data integrity, encryption will be used to keep track of authorship and applicable data will be properly destroyed.

iii. Organization and Interactions

Communication with DSMB members will be primarily through the Principal Investigator (PI), and Office of the Vice President for Research. It is expected that other study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

iv. DSMB Members and Program Staff

All DSMB members will have access to unblinded data when required in order to guide response to serious adverse events. Otherwise, the DSMB will review interim safety data in a blinded manner. The DSMB will decide if unblinding of the arms is necessary based on their analysis of the safety data. The members are independent of the personnel involved in conducting and managing the trial. The DSMB will have a Chair who will provide an unbiased staff interface, especially during executive sessions. The Chair is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes. The DSMB will also have a statistician who is independent of Northwell Health and the study. The statistician will attend closed session meetings.

v. Scheduling, Timing, and Organization of Meetings

DSMB meetings are usually held by remote connections. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study activities, to review and make recommendations about the protocol, and to determine whether data will or will not be masked to identity of randomized groups. Enrollment in this study cannot begin until the DSMB Charter has received IRB approval.

Given the extraordinary circumstance of this study, meetings will be held monthly, with additional meetings or conference calls scheduled as needed.

The agenda for DSMB meetings and calls will be drafted by the Chair. The agenda and meeting materials will be distributed by the Chair two days before each meeting or call.

Before each meeting, when the agenda is sent out, the Chair will ask all DSMB members to state whether they have developed any new conflicts of interest. If a new conflict is reported, the members will determine if the conflict limits the ability of the DSMB member to participate in the discussion, and whether further evaluation of the conflict by the awardee institution for extramural studies, or Northwell ethics officer, is warranted. The DSMB also will review adverse event data (including but not limited to renal impairment, serious skin reactions, QTc prolongation and potential worsening of clinical course of COVID-19), other safety data, enrollment data, and quality and completeness of study data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point.

It is expected that all DSMB members will attend every meeting and call. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one. The Board may wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

vi. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the study investigators and research staff as appropriate, with time for discussion.
- During the **closed sessions**, the DSMB, and research staff, if appropriate and approved by the Chair, will discuss confidential data from the study, including information on efficacy and safety by treatment arm. The DSMB will decide whether to remain masked to the treatment assignments at each meeting.
- The DSMB may elect to hold an **executive session** in which generally only the DSMB members are present in order to discuss study issues independently.

Voting on recommendations will follow Robert's Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert).

If the **closed or executive session** occurs on a conference call or video connection, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the **closed or executive** sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for the PI to ask questions to clarify the recommendations. The meeting is then adjourned.

vii.Reports of DSMB Deliberations

- Formal minutes: The Chair is responsible for the accuracy and transmission of the formal DSMB minutes. These minutes are prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. If concerns are identified, the report will outline the concerns, the board's discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns.

- The DSMB Chair may sign the minutes or indicate approval electronically via email. If there are no concerns or major issues raised, signed minutes will be sent to the PI within 5 days of each meeting or call. If concerns or major issues are raised during the meeting, signed minutes will be sent to the Office Vice President for Research, and the PI within 2 days of the meeting or call. The PI will forward the minutes to the IRB as soon as possible. Subsequently, minutes are included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered final.

viii. Reports to the DSMB

For each meeting, the statistician, with input from research staff if needed, will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

ix. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reason.

x. Assessment of remote monitoring data

At scheduled meetings, the DSMB will review vitals recorded through the Vitaltech interface which are out of range. The DSMB will address patients whose parameters are consistently out of the normal range. After safety review by the DSMB, for these patients the vital sign parameters will be reset to a new range to avoid unnecessary alerts.

Appendix D: Approach

A. Screening of eligible patients (Day 0)

During the screening phase, individuals with SARS-CoV-2 positive tests at the Northwell Laboratory will be identified and approached by the study team with information about the trial via telephone. If they have been symptomatic for Covid-19 for more than 1 but less than or equal to 7 days, they will be educated about the study. Subjects will undergo education about the study, assessment of interest in participating, screening questionnaire, consenting and enrollment through a conference call with the study investigator(s) and study personnel to serve as witnesses.

Here is a script of the screening call:

Study Investigator: Good day Mr/Mrs.X, this is Dr. Y calling from Northwell Health.

Study Investigator: Your name came up as a potential participant for our clinical trial as you had COVID testing performed by the Northwell Health labs. We are calling today to ask you for your consent to determine if you are a candidate for a study on COVID-19. We need your permission to talk to you further about this study.

Study Investigator: Thank you for providing your verbal consent to proceed. We are actively enrolling patients in a randomized, blinded study to determine if famotidine, a medication usually used to treat acid reflux can help treat patients like you with mild to moderate COVID-19. This study will last

approximately 60 days of which we would need your active participation for 28 days. You do not have to come to the hospital to participate. You can participate in this study from the comfort of your home.

If patients indicate that they are upset or surprised by being called, the following script will be used:

Study investigator: I understand your concerns and would like to reassure you that it was not my intention to upset you. We respect your decision not to participate in this research study.

Interested and eligible patients will then undergo the screening questionnaire. During the screening questionnaire, prior to the kits being couriered to them, patients will be asked the following questions on the telephone:

1. Have you ever had trouble swallowing meat or medications including capsules or other pills?
2. Have you ever had trouble with swallowing which has caused you to spit up or cough up food, or medications?
3. Do you experience chest pain when you swallow food or medications?

If they answer yes to any of the above screening questions, these patients will not be eligible for participation in the study. These above questions are loosely based on the Eckardt dysphagia scoring system.[56] Only patients who answer no to all these questions will be consented and enrolled to participate in the study virtually.

B. Consenting

Interested, eligible and screened participants will then be consented to participate. To minimize infected persons from exposing themselves to others, we will enroll subjects remotely to participate in the trial. Informed consent will be obtained remotely via an electronic portal (REDCAP will be utilized as stated previously) or via email or with the telephone through conference call[1]. Additionally, phone number and email address of the patient and one emergency contact will be obtained.

C. Randomization

All patients with confirmed infection with SARS-CoV-2 who meet all other inclusion criteria and none of the exclusion criteria, and who give informed consent will be randomized and enrolled to the treatment or placebo arm. After randomization, we will obtain PROM questionnaire from the patient over the telephone for Day 1 symptom score.

D. Study Kits: Delivery/Orientation (Day 1)

After enrollment, the patient will be couriered the study kit which includes the electronic tablet with the pre-installed VitalCare app, the Bluetooth peripherals (fitness tracker, spirometer, oximeter and scale), the 'trial capsule' and study medications. After receiving the kit, the patients will undergo a virtual orientation with VitalTech to train the patient on how to use the devices followed by index collection of vitals through the Bluetooth devices. This orientation takes approximately 45 minutes and is a service provided by VitalTech.

E. Virtual Visits/Lab draws

After enrollment and orientation, subjects will be followed through the HIPAA compliant VitalCare app. On the day the subjects receive their kits, they will undergo the first virtual visit with the study

investigators. During this virtual visit on Day 1, other baseline assessments will be performed. This assessment includes blood work[2] and spirometry. The patients will perform Day 1 baseline measurements and fill out the "PROM-Questionnaire" on VitalTech Software of the tablet computer under supervision of the study personnel. The PROM questionnaire includes the "extended COVID-19 symptom score" and inquires weight, oxygen saturation, body temperature, spirometry measurements, number of missed doses of the study drug since last filling out the questionnaire, intake of drugs other than the study drug or beforementioned regular medicines, and possible adverse events. To ensure patients can adequately take the study medication, on Day 1, they will be asked to swallow a 'trial capsule' without any active ingredients under the direct supervision of a trial investigator (through the initial virtual visit performed using the VitalCare app). If the patient is able to swallow the 'trial capsule' without any issues, then they will be able to participate in the study. All lab draws and nasal swabs for the subjects will be performed through the remote phlebotomy service, LabFly. We will time the virtual visits and remote lab draws to occur on the same day (on Days 1,7,14,28). If circumstances that lead to exclusion of the patient are identified or it becomes evident that the patient will not be able to execute the tasks necessary for the trial, the patient will be excluded and replaced. Replacement will only take place prior to randomization.

F. Study period

Within 24 hours after enrollment, we expect every patient to take their first of study medication at home. On days 1-14, patients are asked to take the study drug (Famotidine 80mg or placebo) three times daily p.o. On days 1-28, patients will perform oxygen saturation, spirometry and temperature measurements and fill out the PROM questionnaire on the tablet computer or via a phone interview with the study personnel. Patients are asked to report their symptoms and perform the measurements of oxygen saturation, spirometry and temperature every day at 3pm. Weight should be measured in the morning directly after waking up, before breakfast. We will send daily reminders to fill out the PROM questionnaire to the patients at 3pm. These reminders will be sent hourly until the PROM-Questionnaire has been filled in. If the PROM Questionnaire has not been filled out by 6pm, study personnel will reach out to the respective patient via phone to go over the PROM questionnaire and fill out a paper record for that day. If patients for some unforeseen reason, not limited to malfunction of their tablet computer cannot complete their daily PROM questionnaire, they will be advised to call the study coordinator to go over the PROM questionnaire via telephone for that day, a paper record of their PROM questionnaire will then be filled out by study personnel with the patient on the telephone. The collected information will be uploaded to the RedCap data capture site. Also, the fitness tracker will record physical activity[3] on these days and submit it into the VitalTech App via Bluetooth.

G. Remote monitoring of trial participants

We will inform subjects at enrollment and during the study that the remote monitoring of this study does not replace necessary medical care. Subjects will be advised to seek medical care if they feel the need to do so. Daily monitoring of the study participants and the status of their vital data collection including PROM questionnaire(s) will occur remotely through the VitalCare administrator user interface. This is a web based remote monitoring solution provided by VitalTech to help provide oversight of all active trial participants and their current status in the trial. The VitalTech software allows for remote alerts to be generated either when questionnaires are not completed, vitals not collected for the day or if collected physiological measurements are outside the normal range. We will use the following parameters to trigger alerts: heart rate less than 60/min or more than 120/min, oxygen saturation less than 88%, temperature

less than 96 or more than 101 F. Although not real time, this ongoing daily monitoring of the status of the trial participants will ensure timely collection of data. In addition, patients with any abnormal vitals detected during monitoring will be called to follow up and, if there is a clinical concern, they will be advised to report to the nearest emergency room for further care or call 911. When patients cannot be reached their emergency contact will be attempted to be contacted. The daily monitoring will be performed by a designated study investigator. Only physicians who are study investigators will perform the remote monitoring of trial participants. Only study investigators who are licensed in the state of New York will call participants when vitals are detected outside of the normal range.

Visually impaired/individuals unable to use electronic questionnaire on tablet computer: When trial participants cannot utilize the electronic questionnaire to fill out either the initial or daily PROM questionnaire necessary for study participation or completion of the study, study personnel will verbally go over the questionnaire. Study personnel will call such patients daily via telephone to complete the study questionnaire to ensure accurate and complete data collection. These patients will also have a physical copy of the questionnaire for their own reference.

If for some reason a patient chooses to fill out the PROM questionnaire on paper, the already completed questionnaires will be collected through email or fax and transcribed into RedCap by the study personnel.

H. Off-boarding

On Day60, patients will be asked to fill out the PROM-Questionnaire including an assessment of adverse events. After completion of study period, the study kits will remain with the patients.

[1] The screening questionnaire includes:

- patient demographics
- COVID-19 symptom score (See Appendix E)
- History of present illness including number of days since first developing symptoms
- Medical/Surgical History
- Comedication
- current medication with H2-Receptor antagonists
- Patient currently breastfeeding or pregnant

[2] Blood work (Day 1 and 7, and optionally on day 14 and 28 unless stated otherwise) will examine the following markers:

a. hematological markers (including but not restricted to Immune cell activation, of WBC fractions, i.e. neutrophils, monocytes, macrophages, B- and T – lymphocytes, eosinophils, platelets)
b. Organ function, including estimated glomerular filtration rate, AST, ALT, bilirubin, albumin, and coagulation panel
c. Inflammatory markers (including but not restricted to CRP)
d. Organ function, including estimated glomerular filtration rate, AST, ALT, bilirubin, albumin, and coagulation panel
e. D-Dimer
f. Plasma Famotidine Levels

g. PCR copy number on Days 1, 7, 14, and 28
h. Viral Variant on Day 1
i. COVID IgG at Day 1, 7, 14 and Day 28
j. Nucleic acid analyses including but not limited to single cell RNA sequencing of monocytes. This analysis will be performed at Cold Spring Harbor Laboratory.

[3] Physical activity is measured in including but not restricted to heart rate, movement, and energy expenditure

Appendix E: Daily COVID- 19 Symptom Survey

1. In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? *Yes or No*

2. In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? *Yes or No*

Please select a score as an answer for all of the following questions:

0 = none = You were not affected and were able to carry out all usual activities; 1 = mild = You were mildly affected and were able to carry out light work; 2 = moderate = You struggled to carry out any activities other than self-care; 3 = severe = You were severely affected and required help from others for aspects of self-care and/or spent most of the day resting.

3. **Overall symptoms:** In the past 24 hours, what was the severity of your overall COVID-19 symptoms at their worst?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

4. **Lack of energy:** How severely were you affected by lack of energy in the last 24 hours?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

5. **Shortness of breath:** How severely were you affected by shortness of breath in the last 24 hours?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

6. **Cough:** How severely were you affected by cough in the last 24 hours?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

7. **Headache:** How severely were you affected by headache in the last 24 hours?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

8. **Loss of smell or taste:** How severely were you affected by loss of smell or taste in the last 24 hours?
   - 0 = none
   - 1 = mild

- 2 = moderate
- 3 = severe

9. **Loss of appetite:** How severely were you affected by loss of appetite in the last 24 hours?
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

10. **Difficulty of breathing:** How severely were you affected by difficulty of breathing in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

11. **Diarrhea:** How severely were you affected by diarrhea in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

12. **Sore throat:** How severely were you affected by sore throat in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

13. **Muscle pain:** How severely were you affected by muscle pain in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

14. **Hoarse voice:** How severely were you affected by hoarse voice in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

15. **Runny/stuffy nose:** How severely were you affected by runny/stuffy nose in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe

16. **Chest tightness:** How severely were you affected by chest tightness in the last 24 hours?
    - 0 = none
    - 1 = mild
    - 2 = moderate

- 3 = severe

17. **Abdominal pain:** How severely were you affected by abdominal pain in the last 24 hours?
- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

18. **Nausea:** How severely were you affected by nausea in the last 24 hours?
- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

19. **Dizziness:** How severely were you affected by dizziness in the last 24 hours?
- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

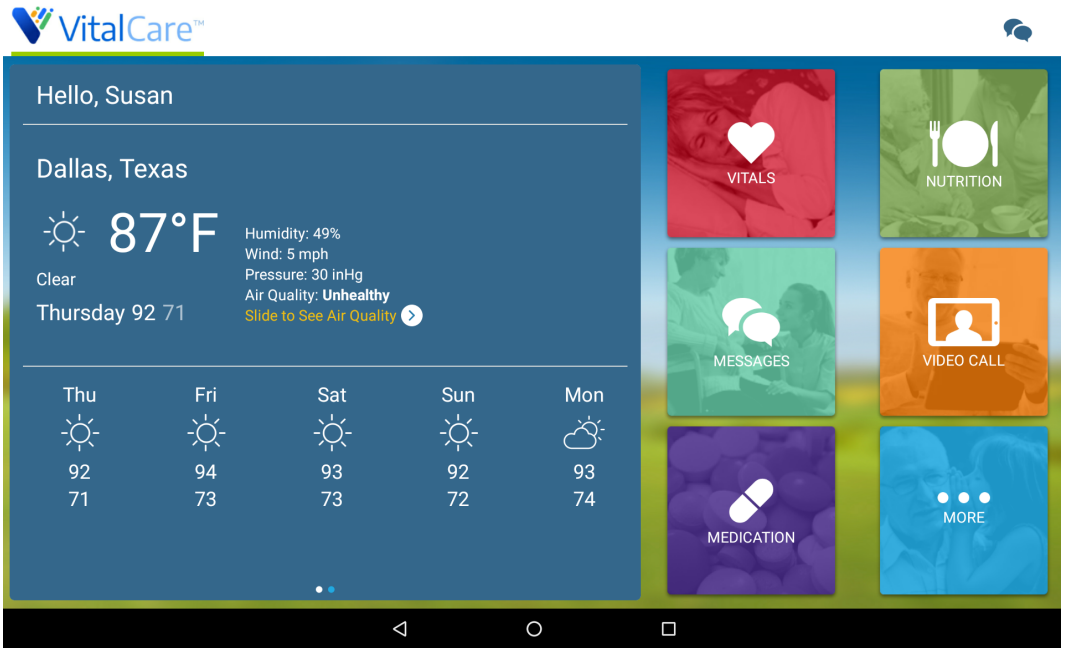
20. **Eye discomfort:** How severely were you affected by eye discomfort (e.g. light sensitivity) in the last 24 hours?
- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

Thank you for completing the survey today!

Appendix F: Preliminary Interface of VitalCare App for this study

xi. VitalCare Landing Page

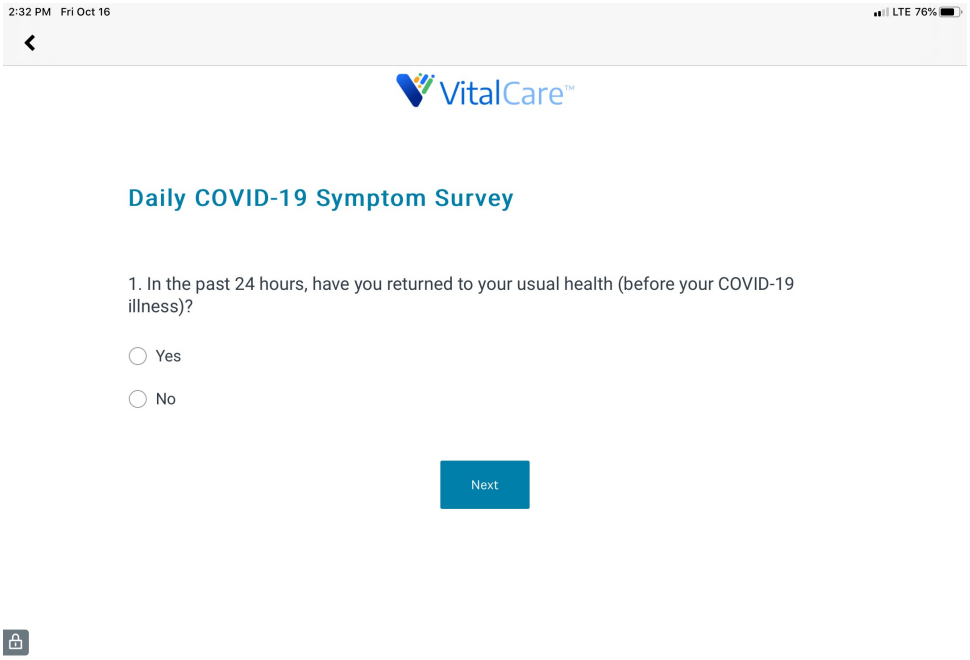
This is the home page which opens when you login to the App. There are 2 sides, one with active information and one with static information



xii. Vitals Page

Displays reading for Vital Signs being captured in the Application from Bluetooth devices or entered manually**.**

xiii. Example survey in the VitalCare App


2:32 PM Fri Oct 16
LTE 76%
VitalCare™
Daily COVID-19 Symptom Survey
1. In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?
Yes
No
Next

Appendix G: Data sheets of devices for patient performed measurements

Weight Scale
WS-CTA-E1

Surface Material	8 mm Tempered Glass
Measurement Range	Up to 500 pounds
Product Dimensions	33 x 33 cm
Battery	AAA x3
FDA Cleared	Yes
CE Cleared	Yes

Bluetooth Connectivity

www.VitalTech.com

Infrared Dual Mode Thermometer
TH-CJU-E1

Display	LCD display with 3 backlit colors: red, green, white
Parameters	0.5 seconds to read temperature. Reads 1-5 cm. Temperature calibration function
Accuracy	± 0.4°F from 96.8-102.2°F or ± 0.2°C from 36.0-39.0°C ± 0.5°F from 89.6-96.7°F or ± 0.3°C from 32.0-35.9°C ± 0.5°F from 102.3-108.0°F or ± 0.3°C from 39.1-42.2°C
Indication	Smart fever alarm with 6 short double beeps (Over 99.5°F or 37.5°C)
Application Range	Forehead mode for all ages, Eardrum mode for children above 1-year old
FDA Cleared	Yes, K172795
CE Cleared	Yes, 7111GB410191220

Bluetooth Connectivity · One Second Reading · Smart Fever Alarm · Hygienic Non Touch · Professional Accuracy · Three Colors Backlight

www.VitalTech.com

Spirometer

Parameters	PEF, FVC, FEV1, FEV1/FVC ratio, FEF25/75, FEV6
Flow Sensor	Bi-directional digital turbine
Flow Range	± 16 L/s
Volume Accuracy	± 3% or 50 mL
Flow Accuracy	± 5% or 200 mL/s
Dynamic Resistance	<0.5 cm H2O/L/s
Product Dimensions	4.29 x 1.93 x 0.82 in
Mouthpiece	0.13 lb
Product Weight	1.18 in
Batteries	AAA x2
FDA Cleared	Yes, K072979
CE Cleared	Yes, MED 9826 by Kiwa-Cermet

Bluetooth Connectivity

www.VitalTech.com

Pulse Oximeter
PO-CJU-E1

Display	OLED Screen
Parameters	Pulse Rate, SpO2, Perfusion Index
Direction	4-Direction Display with 6 modes
Accuracy	Pulse Rate: 30~99 bpm, ± 2 bpm SpO2: 70%~100%, ± 2% Perfusion Index: 0.2~1.0%, ± 0.2 digits 1.1~20.0%, ± 20%
Battery	AAA x2
Dimensions	62 x 37 x 32mm
Weight	28.7g without batteries
Indication	Real-time battery status, Weak or unstable signal, Value limit remind, Adjustable brightness
FDA Cleared	Yes, K170965
CE Cleared	Yes, 7111GB410191220

Pulse Rate Measuring · Bluetooth Connectivity · Guaranteed Accuracy

www.VitalTech.com

Appendix H: Data collected as part of VitalTech assessment

Category	Data Point
Home	Calls
Home	Alerts
Home	To-Do
Home - Alert Queue	Patient trial ID
Home - Alert Queue	Alert Type
Home - Alert Queue	Time /Date
Home - Alert Queue	Vitals
Home - Alert Queue	Actions
Home - Alert Queue	Communication (Call / Video)
Home - Call	Patient trial ID
Home - Call	Time in Queue
Home - Call	Request time
Home - Call	Vitals
Home - Call	Call Request
Home - Call	Actions
Home - To-Do	My Tasks
Home - To-Do	To Do
Home - To-Do	In Progress
Home - To-Do	Patient trial ID
Home - To-Do	Active Time
Home - To-Do	Task Description
Home - To-Do	Actions - Complete
Home - To-Do	Actions - Revert
Home - To-Do	Actions - Grab
Home - To-Do	Actions - Edit
Home - To-Do	Assigned To
Active Users - Vitals	Heart Rate
Active Users - Vitals	Sp02
Active Users - Vitals	Weight
Active Users - Vitals	Caloric Burn
Active Users - Vitals	Step Count
Active Users - Vitals	Temperature
Active Users - Vitals	FEV
Active Users - Vitals	FVC

Active Users - Vitals	FEV/FCV
Active Users - ADLs	Medication
Active Users - Medication	Drug
Active Users - Medication	Dose
Active Users - Medication	Route
Active Users - Medication	Time
Active Users - Vitals Theresholds	Heart Rate
Active Users - Vitals Theresholds	Sp02
Active Users - Vitals Theresholds	Caloric Burn
Active Users - Vitals Theresholds	Step Count
Active Users - Vitals Theresholds	Temperature
Active Users - Vitals Theresholds	FEV
Active Users - Vitals Theresholds	FVC
Active Users - Vitals Theresholds	FEV/FCV
Active Users - ADD NEW Patient	Gender
Active Users - ADD NEW Patient	Weight (lbs)
Active Users - ADD NEW Patient	Height (Feet and inches or cm)
Active Users - ADD NEW Patient	Patient ID
Active Users - ADD NEW Patient	Tags
Active Users - ADD NEW Patient	Community
Active Users - Log	RPM Time Entry
Active Users - Log	Note
Active Users - Log	Other Time Entry
Active Users - Log	Alert
Active Users - Log	Thereshold
Active Users - Log	Login
Active Users - Log	Form
Active Users - Log	Call History
Active Users - Log	Daily Medication
Active Users - Log	Medication
Active Users - Log	Push Notification
Active Users - Log	Register User
Active Users - Log	Survey Request
Active Users - Log	Survey Response
Active Users - Log	Update User
Active Users - Log	User Alert
Active Users - Log	User Alert Update Status Resolved
Active Users - Schedules	Medications

Active Users - Schedules	Announcements
Active Users - Schedules	Group Announcements/Questions/Surveys
Active Users - Survey	Survery Title
Active Users - Survey	Description
Active Users - Survey	Created Date & Time
Active Users - Survey	Responded Date & Time
Active Users - Survey	Status
Active Users - Config/Devices	Installed Devices
Messages	In Box
Messages	Search (patient)
Messages	Message viewing screen
Messages	Attachments
POP	Patient Name
POP	Patient Demo status
POP	On-boarding Date
POP	Enrollment Date
POP	First Vitals
POP	Last Vitals
POP	Patient Status - Active / Archive/ Pause/ Deceased