MEDICAL PROTOCOL (HRP-590)
SHORT PROTOCOL TITLE: Randomized control trial of losartan for outpatients with COVID-19
VERSION DATE:5APR2020

Protocol Title	Randomized Controlled Trial of Losartan for outpatients with COVID-19
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.7	3/26/20	Changes to I/E criteria, method of patient identification and screening procedures, data collected, and corrected inconsistencies. Additional sites added. Additional blood testing and home blood pressure cuffs added	Y – updated biospecimens and risks
1.8	3/31/20	Clarified I/E criteria, added stopping rules, expanded eligible clinics, clarified table of procedures, clarified reporting of protocol deviations	No

ABBREVIATIONS/DEFINITIONS

- COVID-19 Disease caused by the virus SARS-CoV-2, or “Wuhan coronavirus”
- ACE2 Angiotensin converting enzyme 2
- ACE Angiotensin converting enzyme
- ACEi Angiotensin converting enzyme inhibitor
- AE Adverse event
- ALI Acute lung injury
- ARDS Acute Respiratory Distress Syndrome
- ARF Acute respiratory failure
- ARB Angiotensin receptor blocker
- AT1R Angiotensin 1 receptor
- CDR Clinical Data Repository
- CDSS Clinical decision support systems
- CTSI Clinical and Translational Science Institute
- D & I Dissemination and Implementation
- DUA Data Use Agreement
- EBP Evidence-based best practice
- eConsent Electronic consent
- ECMO Extracorporeal membrane oxygenation
- ED Emergency department
- EHR Electronic health record
- FiO2 Fraction of inspired oxygen
- FV Fairview Hospital System
- HCMC Hennepin County Medical Center
- ICD International Classification of Diseases
- ICF Informed Consent Form
- ICS Informatics Consulting Service
- ICU Intensive care unit
- LOS Length of stay
- MHealth University of Minnesota Health
- NETT Neurological Emergencies Treatment Trials
- PaO2 Partial pressure of arterial oxygen
- SAE Severe adverse event
- PETAL Prevention and Early Treatment of Acute Lung injury
- SaO2 Saturation of oxygen
- SIREN Strategies to Innovate Clinical Trials Network
- SOFA Sequential organ failure assessment
- UMMC University of Minnesota Medical Center

Table of Contents

1.0 Objectives

1.1 *Title*: Randomized Controlled Trial of Losartan for outpatients with COVID-19

1.2 *Purpose:* To determine the impact of losartan compared to placebo on the rate of hospitalization in outpatients diagnosed with COVID19 not requiring hospital admission at the time of initial presentation.

1.3 *Hypothesis:* Losartan will significantly reduce the rate of hospitalization at 15 days in outpatients not requiring hospitalization after initial presentation.

1.4 *Study design:* Multi-center, prospective, randomized blinded interventional trial of losartan (25 mg orally twice daily) versus placebo administered for 10 days or until hospital admission.

1.5 *Study procedures:*

- The trial emphasizes early intervention to prevent the progression of respiratory disease. Patients presenting to the emergency department or outpatient drive-thru COVID-19 clinics who test positive for the virus will be eligible for enrollment and randomization within 72 hours of test result and no more than 7 days from symptom onset.
- Investigators and research coordinators will leverage already functional electronic consent procedures to enroll patients safely while also minimizing risk to study staff. Patients tested at all locations will be given a brochure with study information instructing them to contact the study team if interested in a clinical trial (see attached patient-facing study related materials). In addition, patients receiving test results by phone from the clinical care team will be alerted they may qualify for a research study and that study team members may contact the patient about eligibility. The patient may opt-out of such followup calls.The eConsent platform is currently used in NIH supported StrokeNet and SIREN clinical trials, and are HIPAA compliant.
- Enrolled patients will be randomized to losartan or placebo, and undergo daily assessment by study personnel with built-in safety and efficacy assessments. Enrolled participants will be delivered study drug, a thermometer, oropharyngeal swabs, home blood pressure cuff, and a urine pregnancy test, if applicable, by courier service within 24 hours of randomization. Study personnel will call patients every other day during the intervention window to review study drug adherence, review symptoms for possible adverse events, remind patients to collect oropharyngeal swabs, and administer validated outpatient dyspnea assessments at predetermined time points.
- Patient-collected oropharyngeal swabs will be retrieved using a courier service with capacity for transport of biologic specimens to a BSL-3 laboratory (https://www.researchservices.umn.edu/services-name/biosafety-level-3-program). These will be stored for public health and viral research purposes.
- Patients will be followed for 90 days to determine outcomes and the presence of any delayed adverse events. Follow-up phone contact and

electronic medical record review will determine the primary and secondary efficacy endpoints, and provide additional safety data.

1.6 Data and specimen collection method

- Inclusion and exclusion criteria, patient demographics, baseline comorbidities, symptoms, and validated symptom assessment measurements by patient self-report, obtained in the medical record, or obtained during an in person pre-screening visit will be collected at the time of enrollment and maintained in a RedCap database. In addition, electronic consent forms will be maintained in a University of Minnesota RedCap database with established functionality currently used by our group for this purpose in our group. The database, with the currently approved eConsent policy, and is HIPAA compliant.
- Every other day follow-ups will be recorded by study personnel into a RedCap database and will include self-reported AEs and medication adherence and maximum daily temperature. On days 0, 4 and 10, a previously validated patient-reported outcomes measurement information system (PROMIS) dyspnea survey and SF-12 (survey's attached in supplement). In the event the patient is not available or contacted on the day of survey administration, surveys administered +/- 1 day will be considered before this data point is considered missing. The following datapoints will also be collected, if available:
    - Name
    - Date of birth
    - Medical record number (if applicable)
    - Phone number
    - Email address
    - Age
    - Gender
    - Race
    - Ethnicity
    - Insurance status (if available)
    - Zip code
    - Location of initial sample collection for diagnosis
    - Location of assessment
    - Date and time of initial sample collection for diagnosis
    - Date and time of positive test result for COVID-19
    - Date of first symptoms
    - Date of first fever (temperature >101.5)
    - Vital signs at presentation (if recorded)
    - Clinical laboratory results at presentation (if recorded)
    - Patient-reported comorbidities [hypertension (requiring or not requiring medication), diabetes mellitus (insulin or non-insulin dependent), coronary artery disease, myocardial infarction, congestive heart failure (with preserved or reduced ejection fraction, if known), pacemaker or AICD, asthma (with or without emergency department evaluation and / or hospital admission in the past year), chronic obstructive pulmonary disease, chronic bronchitis, chronic steroid use, history of transplant (with type),

arrhythmias including atrial fibrillation, dialysis, angina, pulmonary hypertension and obstructive sleep apnea, renal disease, liver disease, tobacco and alcohol use history, recent pregnancy or breastfeeding history, height and weight]
- Self-reported home medications [antihypertensives, insulin, non-insulin diabetes medications, corticosteroids (inhaled or systemic), other immunosuppressants hydroxychloroquine, other COVID-directed treatments] or home oxygen use
- Use of outpatient COVID-directed treatments (such as hydroxychloroquine, Tylenol, ibuprofen, azithromycin, or others)
- PROMIS Pool v1.0 Dyspnea Characteristics Survey (5 question Likert scale survey) (attached) with date/time of administration
- Short form 12 (SF-12) health survey (attached) with date/time of administration
- Oropharyngeal swab every third day (performed, yes or no)
- Lowest home blood pressure daily
- Highest home temperature daily
- Medication adherence
- Hospital admission (with date, if applicable)
    a. If admitted: initial vital signs, initial and highest method of respiratory support (oxygen by nasal cannula, facemask, high flow nasal cannula, CPAP, BIPAP, endotracheal intubation, ECMO), initial and worst measures of organ failure (SOFA score), and initial and worst markers of cardiac injury (troponin, BNP/pro-BNP. CXR or CT chest results will be recorded. If patients are admitted to non-MHealth or HCMC hospitals, we will contact the patient to obtain permission to request data from their hospitalization.
- Date of death (if applicable)
- Study withdrawal, with date and time (if applicable)

- Final outcome follow-ups will be determined through a combination of patient report, electronic medical record review, and review of the social security death index (SSDI).

- All data will be stored in a password protected Redcap database, with customizable tiered access and an audit trail. All protected health information (PHI) will be marked with a PHI tag that will prevent export, so only deidentified data can be exported from the database. Only de-identified data sets with all PHI removed will be shared for the purposes of data analysis.

- Oropharyngeal swabs will be patient-collected and placed in pre-packaged transport to be collected by a biosafety-trained courier service, transported and processed to the University of Minnesota BSL-3 lab, and frozen at -80 C until later analysis. All biospecimens will be labeled with a deidentified patient ID number to prevent inadvertent disclosure of PHI. The following data points will be collected for biospecimens:
    - Study ID number
    - Day of protocol

- Specimen tracking number

2.0 Background

2.1 Significance of Research Question/Purpose:

Since appearing in Wuhan, China in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused disease (COVID-19) in over 155,000 people with over 5,900 deaths to date across 100 countries.[1-3] The mortality is estimated at 3.7%,[4] with infectivity (R0) estimated at 2.24 to 3.585,[5] with morbidity and mortality disproportionately affecting the elderly.[6] Most severely affected patients are admitted for respiratory support and die of respiratory failure.[7,8] At present there is no current specific treatment for patients with COVID-19.[9] The novel coronavirus is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV) which caused an outbreak of disease (SARS) in 2003; this may inform the development of novel treatments.[9,10] Attempts to develop vaccines since SARS or middle eastern respiratory virus (MERS) have been unsuccessful, will take time, and may or may not be effective for this or future coronavirus pandemics.[11] Extensive efforts to date, therefore, have been appropriately focused on screening, identification, and containment with collaboration and coordination within and between governments to combat its spread.[12]

Due to the nature of coronavirus cellular binding, there exist several promising novel pharmacotherapeutic strategies that differentiate this virus from seasonal or pandemic influenza. Similar to the 2002-2003 SARS-CoV, the SARS-CoV-2 virus binds the spike protein of angiotensin-converting enzyme 2 (ACE2), a critical component of the renin-angiotensin-aldosterone (RAAS) system, in order to enter the cell.[13] **(Figure 1 – red arrow on right)** Multiple proposed interventions to combat SARS-CoV-2 under development focus on this pathway with the goal of blocking viral entry into cells, and include anti-viral agents,[14] anti-malarial medications,[15] vaccines,[16] and viral protein inhibitors.[9] While these therapies are promising, immediate use of these interventions are not feasible. In many cases, drugs are still under development and lack a clinical indication, with limited safety and efficacy data in humans to date. These factors will necessarily lead to delays in drug development. Given the rapid spread of SARS-CoV-2, patients would greatly benefit from interventions

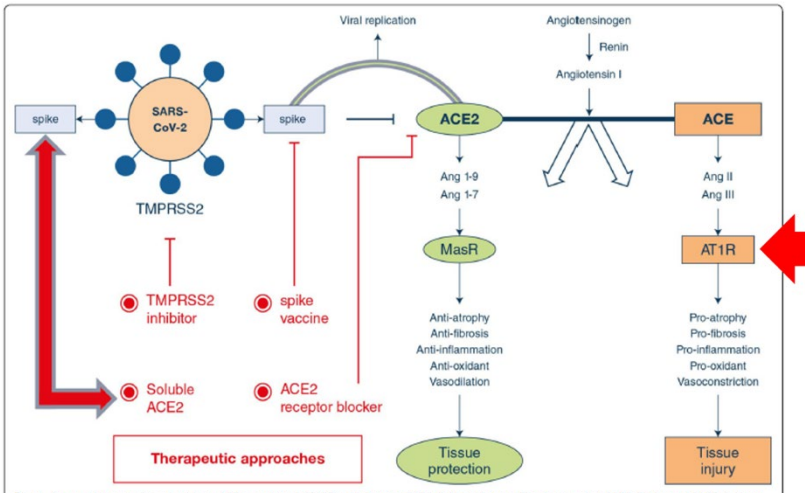


Fig. 1 Potential approaches to address ACE2-mediated COVID-19 following SARS-CoV-2 infection. The finding that SARS-CoV-2 and SARS-CoV use the ACE2 receptor for cell entry has important implications for understanding SARS-CoV-2 transmissibility and pathogenesis. SARS-CoV and likely SARS-CoV-2 lead to downregulation of the ACE2 receptor, but not ACE, through binding of the spike protein with ACE2. This leads to viral entry and replication, as well as severe lung injury. Potential therapeutic approaches include a SARS-CoV-2 spike protein-based vaccine; a transmembrane protease serine 2 (TMPRSS2) inhibitor to block the priming of the spike protein; blocking the surface ACE2 receptor by using anti-ACE2 antibody or peptides; and a soluble form of ACE2 which should slow viral entry into cells through competitively binding with SARS-CoV-2 and hence decrease viral spread as well as protecting the lung from injury through its unique enzymatic function. MasR—mitochondrial assembly receptor, AT1R—Ang II type 1 receptor

***Figure 1**: Mechanisms of Action of SARS-CoV-2 interaction with the Renin Aldosterone Angiotensin System and possible therapeutic options proposed by Zhang et al.[9]*

with a well-established safety profile readily available for immediate clinical trial testing and rapid knowledge translation if efficacious.

2.2 Rationale and Scientific Hypothesis:

Renin-aldosterone blockade has been proposed as a potential treatment for COVID-19.[17-19] This hypothesis was originally published by Sun et al[19] on February 16, 2020 (manuscript published in Chinese) and in the British Medical Journal on February 4, 2020.[18] This hypothesis was reinforced in Drug Development Research on March 4, 2020.[17] To the best of our knowledge, our study is the first investigating this hypothesis.

As opposed to ongoing clinical trials targeting viral binding and entry, the proposed clinical trial proposes to mitigate the respiratory consequences of SARS-CoV-2, thereby reducing morbidity and mortality. As illustrated in Figure 1, SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2), similar to 2002-2003 SARS-CoV. Molecular simulation has shown SARS-CoV-2 has a higher affinity for ACE2 compared with SARS-CoV.[20]

Healthy State:

In states of health, ACE2 converts Angiotensin 2 (ATII) into lung-protective angiotensin (AT) 1-7 and 1-9, thus preventing unopposed ATII activation of AT1R. Unopposed AT1R activation triggers a downstream pro-inflammatory cascade, characterized by increased lung permeability, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and death **(Figure 2).**[4,18] AT1R activation also leads to type II pneumocyte apoptosis, a common feature of ARDS.[12,13] Therefore, under usual conditions of health, ACE2 prevents lung injury.

Infection with SARS-CoV-2:

Impaired ACE2 activity due to binding with SARS-CoV-2 results in excessive ATII allowing unopposed binding of AT1R without generation of lung-protective AT1-7 and AT1-9 **(Figure 2)**.[21,22] An ongoing clinical trial is attempting to exploit this mechanism by treating 24 patients with recombinant human ACE2 (rhACE2) infusions.[23] Infusions of ACE2 have previously been shown to result in decreased AT2 and increased AT1-7.[24] Unfortunately, protein recombinant human infusions are costly and scaling production will take significant time.

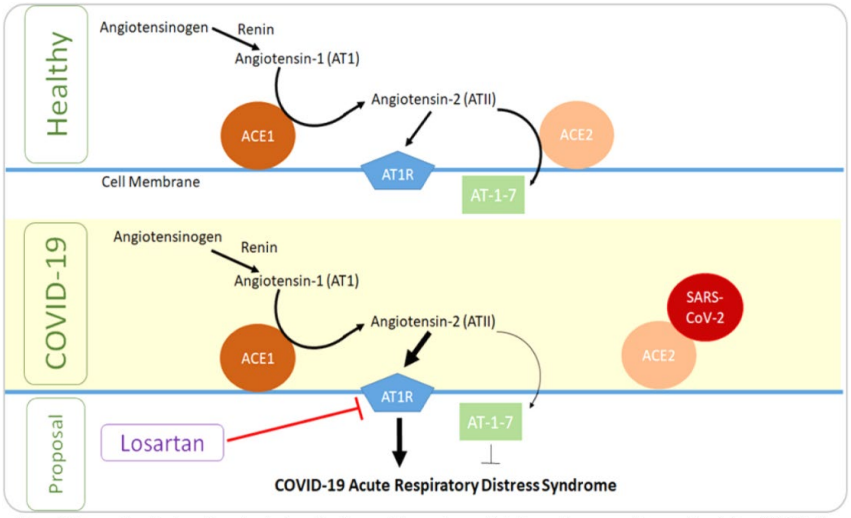


***Figure 2**: Proposed mechanism of Losartan in disrupting the pro-inflammatory and injurious pathway caused by over stimulation of AT1R in the setting of SARS-CoV-2 infection. ACE1-Angiotensin converting enzyme 1, AT1R-Angiotensin I receptor, ACE2-Angiotensin converting enzyme 2, AT1-7-Angiotensin 1-7.*

Given this, we propose to leverage a readily available angiotensin receptor blocker (ARB) with an excellent safety profile, losartan, to mitigate this pathway with the aim of

decreasing ALI/ARDS. While ACE inhibitors (ACEi) could also be considered for trial, ACEi are frequently associated with cough which could exacerbate the spread of the disease. In 2 8 week studies, studies, losartan had 17% and 27% rates of cough vs 69% and 62% (see package insert). Furthermore, ACE inhibitors can induce expression of ACE2 secondary to low local angiotensin II levels, potentially increasing viral uptake.

Preclinical Supporting Data:

SARS-CoV specific preclinical work:

In 2003, ACE2 was identified as the binding protein for SARS-CoV.[25] This was validated in 2005 by Kuba et al. This same study identified that SARS-CoV injury worsens acute lung injury and can be attenuated by Renin-Angiotensin (RAS) pathway inhibition.[22] Kuba first identified that ACE2 knockout mice had significantly lower viral loads in the lung following infection, whereas wildtype (wt) mice had very high viral loads.[22] Additionally, wt mice had significantly higher lung injury scores following SARS-CoV infection.[22] SARS-CoV infection results in downregulation of its binding protein ACE2 (ACE2 has been shown to be lung protective in its action of converting AT2 -> AT1-7).[22] This finding that SARS-CoV results in downregulation of ACE2 has been validated in subsequent studies.[26] Kuba et al, then showed that treatment with Losartan 15 mg/kg attenuated lung injury (**Figure 3B)** and the development of pulmonary edema **(Figure 3C)** in mice infected with SARS-CoV Spike-FC.[22] For this study 2.5-3 month old mice received SARS-CoV Spike-FC. 30 minutes later they received HCL to expedite lung injury. Mice were then randomized to Losartan vs vehicle. 1 and 2 hours later SARS-CoV Spike-FC. Mice then received 3 hours of mechanical ventilation and were sacrificed. **(Figures 3B and C).** [22]

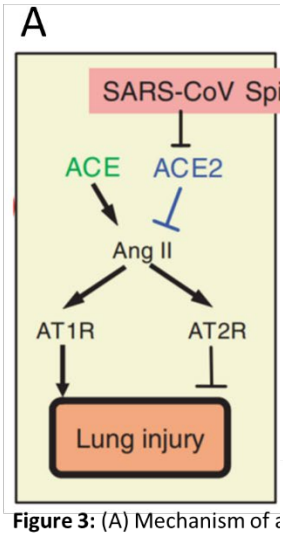


Figure 3: (A) Mechanism of a
(green diamond) treated wit
receptor inhibitor (Losartan)
Angiotensin II receptor inhib
Figures from Kuba et al, Nat

In 2005, Imai et al showed that loss of ACE2 leads to significantly worse

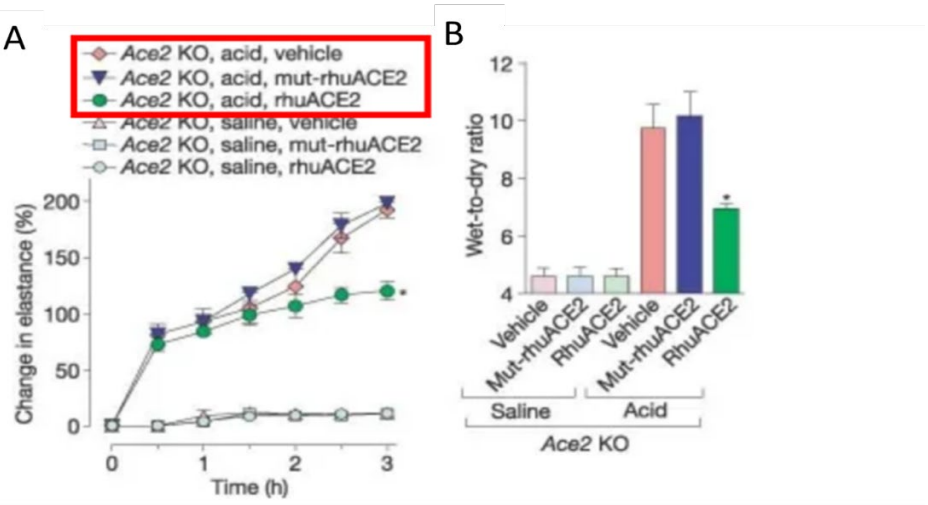


Figure 4: (A) ACE2 knockout (KO) mice treated with recombinant ACE2 (rhuACE2) verses vehicle or mutant rhuACE showed reduced lung injury (B) ACE2 knockout (KO) mice treated with recombinant ACE2 (rhuACE2) verses vehicle or mutant rhuACE showed reduced wet/dry ratio
Figures from Imai et al, Nature, 2005

oxygenation, massive lung edema, and inflammatory cell infiltration in mice compared to wildtype mice in response to acid aspiration.[21] They then performed a rescue experiment and showed that supplementation with rhACE2 rescued infected mice **(Figure 4A, B: green circles vs purple triangle and dark pink diamond)**.[21]

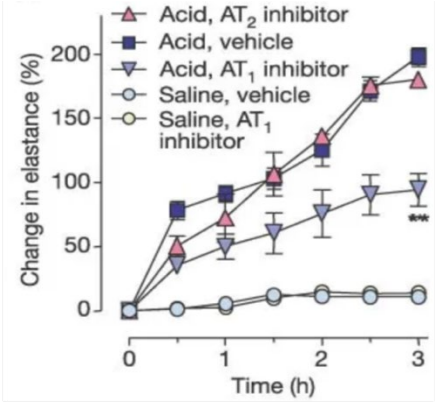


Figure 5: (A) ACE2 knockout (KO) mice treated with acid-induced ARDS treated with AT2R inhibition (pink triangle), AT1R inhibition (light purple triangle), or vehicle (purple square). *Figures from Imai et al, Nature, 2005*

Imai et al. demonstrated inhibition of AT1R via losartan reduced lung injury **(Figure 5, light purple triangle)** compared with vehicle **(Figure 5, purple square)**. This pathway was specific to inhibition of AT1R as, inhibition of AT2R did not reduce lung injury **(Figure 5, pink triangles)** For this study ACE2 knockout (KO) mice were given AT1R (losartan) or AT2R 30 minutes prior to acid-induced acute respiratory distress syndrome (ARDS).[21]

<u>Preclinical supporting data for Renin-Angiotensin inhibition in other viral pneumonias that interact with ACE2:</u>

Both influenza H7N9 and H5N1 have been implicated to cause lung injury through ACE2 with resultant upregulation of angiotensin-2 and AT1R induced lung injury (Zou et al., Nature Communications, 2014 and Yang et al, Sci Rep, 2014).[27,28] Yiwu et al found that Losartan at <u>doses equivalent to those used for clinical treatment of humans</u> were associated with increased survival, decreased lung edema and lung injury scores, and decreased IL-6 for mice infected with H5N1 **(Figure 6 A-E)** (Yiwu et al, Sci China Life Sci, 2015).[29]

Yang et al infected 4-week-old mice with either influenza H7N9 or placebo.[28] Mice were given Losartan 30 minutes prior to viral infection. They identified that inhibition of AT1R attenuates H7N9 lung injury and was associated with lower wet-dry ratios and lower infiltrative cell counts (Yang et al, Sci Rep, 2014).[28]

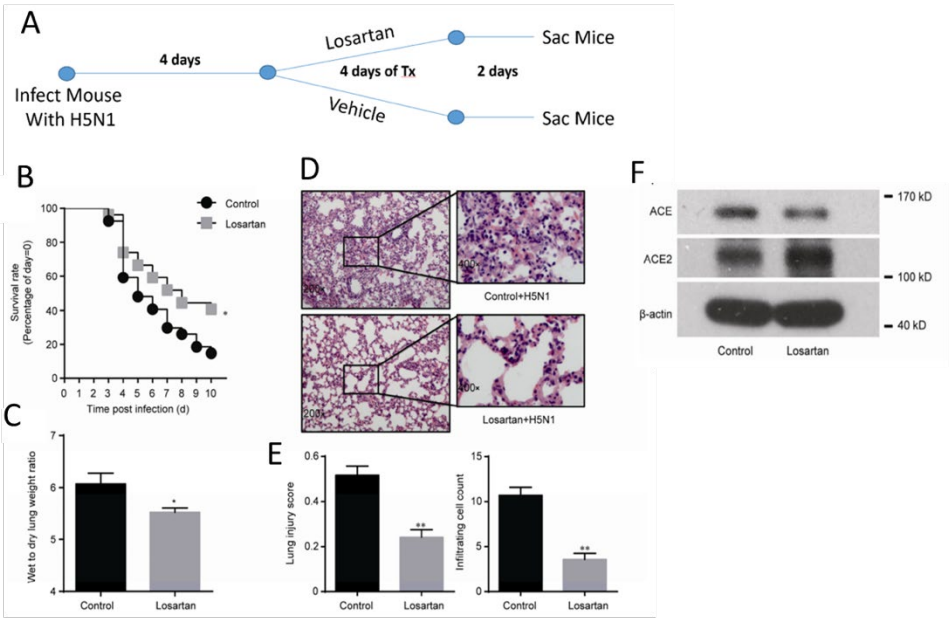


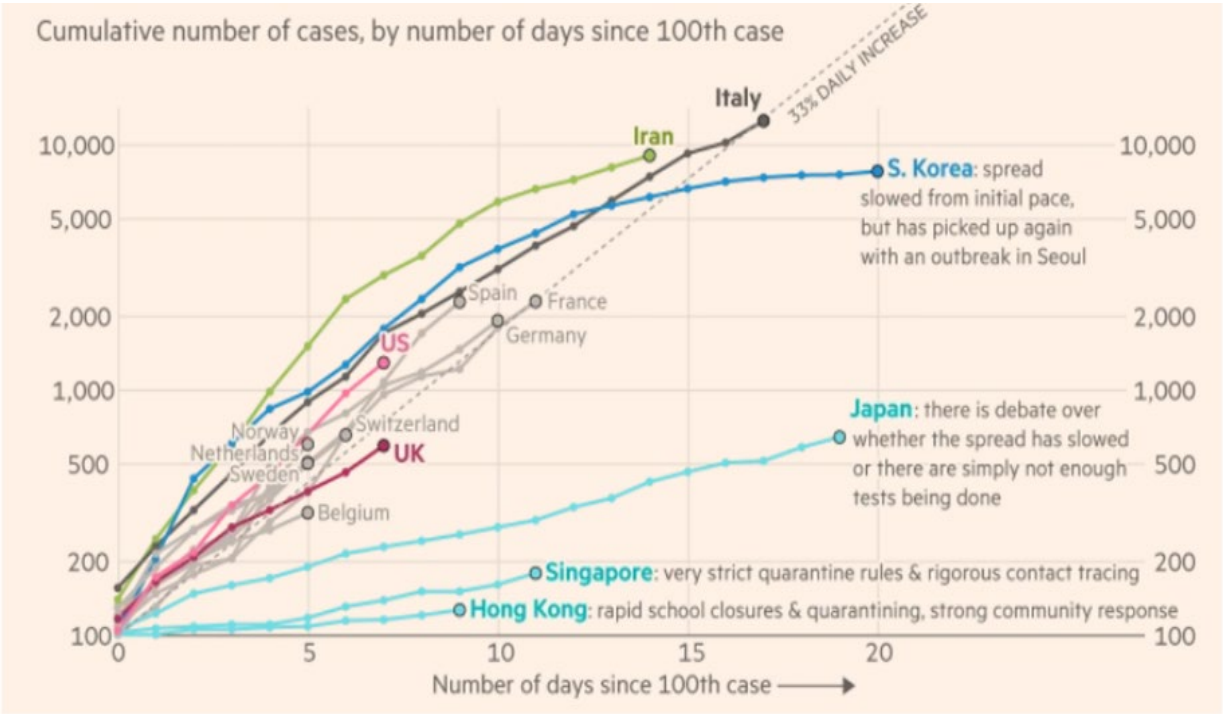
Figure 6: (A) Study Design (B) Mice infected with H5N1 had improved survival when treated with losartan verses control (C) Mice infected with H5N1 had less pulmonary edema when treated with losartan verses control (D) Mice infected with H5N1 had decreased pulmonary inflammation when treated with losartan verses control (E) Mice infected with H5N1 had reduced lung injury score when treated with losartan verses control (F) Mice infected with H5N1 had increased ACE2 (lung protective) and reduced ACE1 (lung deleterious) when treated with losartan verses control. *Figures from Yiwu et al, Sci China Life Sci, 2015*

2.3 **Existing Literature:**

There is no existing literature regarding the effect of losartan in COVID-19. **To that effect there is limited literature regarding the effectiveness of any treatments on COVID-19.** Data of relevance to are summarized in 2.1-2.3.

There is an urgency to identify effective and readily available treatments for patients with COVID-19. This proposed study will elucidate the role of losartan, this is based on strong physiologic and preclinical data as described in detail above.

There is a <u>critical and dire</u> need to identify and <u>evaluate all possible methods to minimize the burden of COVID-19</u> on our society and healthcare system. At the current rate of growth (as of 3/13/2020) America is 1 week from widespread outbreak similar to Italy and Iran. Unfortunately, current community efforts are not sufficiently slowing down spread as our slope (see Figure below) is higher in the last few days than the rest of the world.



3.0 Study Endpoints/Events/Outcomes

3.1 *Primary Endpoint/Event/Outcomes:* The primary endpoint is the need for hospital admission at 15 days from randomization.

3.2 *Secondary Endpoint(s)/Event(s)/Outcome(s):*

- Subjective improvement in dyspnea as measured by the dyspnea PROMIS measures (survey attached) at day 0, 4 and 10
- Daily maximum temperature
- Number of emergency department or clinic presentations within 28 days
- Disease severity rating on the *7-point ordinal scale* [Time Frame: Day 7, 15, 28]
    - The *7-point ordinal scale* is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities
- Change in viral load by oropharyngeal swab
- Ventilator free days, oxygen free days
- Need for hospital admission and oxygen therapy at 15 days

3.3 Justification of the primary outcome: This trial seeks to mitigate lung injury from COVID-19 rather than treating the viral infection. Most patients present to the hospital secondary to dyspnea and pneumonia, and the primary mechanism of death is via respiratory failure progressing to multi-system organ failure. Prevention of acute lung injury with an angiotensin receptor blocker such as losartan may reduce the development of the primary need for hospitalization. **This is a clinically relevant outcome not only to patients, but also to the healthcare system due to overwhelming surge of patients straining hospital resources which not only puts patients with COVID-19 at risk, but also those admitted to the hospital for other reasons**. It is important to emphasize the critical need for research studies that identify effective treatments that mitigate the progression of disease requiring hospitalization. **To provide a specific example**, Minneapolis has a metropolitan population of 3.4 million residents with approximately 5000 inpatient hospital beds and 500 ICU beds. If only 1% of the Minneapolis population developed symptomatic COVID-19 that would equate to 34,000 patients. Studies support a 13-15% hospitalization rate both in the US (as of the time of this writing New York state has 421 cases, 50 hospitalized, 13 in ICU) and internationally[30] which would constitute 4420 – 5100 beds, nearly the entire metropolitan hospital capacity.

3.4 Justification of the secondary outcomes: Validated study instruments to assess dyspnea and physical function will assess patient-centered outcomes and strengthen the biologic plausibility of the intervention. A decrease in inflammation through the reduction of pulmonary edema may be observed as a change in fever. The study drug could affect the number of presentations requiring evaluation but not result in hospital admission. The 7-point ordinal scale described is used by other ongoing COVID-19 clinical trials and will allow harmonization of the trial results.

4.0 Study Interventions / Interventional Agents

4.1 *Intervention arm:* The intervention is losartan, an angiotensin receptor blocker, in microcrystalline methylcellulose, administered at 25 mg PO twice daily for 10 days (patients with eGFR 30-60 mL/min/1.73 m^2 will be given 25 mg once daily) or until hospital admission, whichever comes first.

- *Rationale for the duration of the intervention:* The average time from symptom onset to hospitalization based on reports to date is 8-9 days.[7,31] We expect participants to present with at least 1-2 days of symptoms. We expect most participants to reach their primary endpoint within 10 days of treatment (11-12 days from symptom onset), which represents our time of maximal efficacy of the intervention in this cohort. We have chosen to stop treatment at the time of hospitalization as the participant may or may not be admitted to a participating hospital, introducing significant logistical limitations.
- *Rationale for the dose of treatment:* The lowest dose of losartan is 25 mg orally, which minimize risk of side effects and AEs to the patient. The maximum clinical dose is 100 mg daily. Losartan has a half-life of 2 hours with an active metabolite E3174 of 6-9 hours. The threshold for blockade of angiotensin-II receptor is at least 20 mg per day.[32] Twice daily dosing has been shown to potentiate angiotensin-II receptor blockade compared with once daily dosing. We propose a dose of 25mg twice daily. At this dose, extrapolated data suggest 37% inhibition of angiotensin-II receptors, which we believe represents an excellent risk: benefit ratio for trial participants. At the highest maximum allowable clinical dose (50 mg twice daily) we would anticipate 50% inhibition of angiotensin-II receptor.[32] Multiple early pharmacokinetic studies of losartan at the low-dose demonstrates the drug has minimal side effects on blood pressure (consistently <10 mmHg reduction in maximal systolic blood pressure) in healthy patients[33-36] without an overactive renin-angiotensin-aldosterone system. Clinical exclusion criteria has been added to identify patients who might be at increased risk for side effects. Patients with moderate renal dysfunction (eGFR 30-60 mL/min/1.73 m^2 will be given 25 mg once daily given impaired renal clearance.

4.2 *Placebo arm*. Placebo capsules will match, and contain microcrystalline methylcellulose only.

4.3 *Investigational new drug.* The study will undergo pre-IND review with the Food and Drug Administration to determine the need for an investigational new drug assessment, and will be assigned an IND number if required.

4.4 *Timing of the intervention:* Treatment will continue for 10 days or attainment of the primary outcome (hospital admission).

4.5 *Duration of study participation:* The final follow-up will occur at 90 days after randomization to determine episodes of delayed hospitalization. Data analysis is expected to be completed within 1 year of enrollment of the final patient.

4.6 *Drug Handling, blinding, and randomization:*
Fairview Investigational Drug Services (IDS), part of M Health Fairview will oversee the preparation of treatment drug and placebo. Identical pills (#20) will be placed in identical

bottles with a deidentified study number coded by site and patient number (e.g. 01-001, 02-001, etc.). A site-specific randomization schema will be created (each site will undergo permuted block randomization with random block sizes stratified by site and age). Given significant differences in outcome by age, patients will be randomized by age strata (>=50, <50). Randomization allocation will be 1:1. IDS will not be blinded to patient randomization. All other members of the study, the participants, and the clinical care team will be blinded to treatment allocation.

4.7 *Provision of study drug to patients:* Following randomization, a courier service will ship drugs to study participants within 24 hours of randomization. Each dispensing will contain 20 capsules, enough to complete the 10-day therapy

4.8 *Study unblinding:* MHealth Fairview, East bank Inpatient Pharmacy UMMC campus, will hold the blind for all subjects on study. In the event of an emergency and unblinding is necessary, study staff can contact 612-273-3066, option 1, then option 2. This information is included on each label.

4.9 *Biosafety*: N/A. The intervention is not a biohazard.

4.10 *Stem Cells:* N/A

4.11 *Fetal Tissue:* N/A

4.12 *Use of radiation:* N/A

4.13 *Use of Center for Magnetic Resonance Research:* N/A

5.0 Procedures Involved

5.1 *Screening:* Screening logs containing non-identifiable information (age, gender, race, ethnicity, location of presentation, and reason for exclusion) will be maintained for patients screened but not enrolled. Patient screening will follow one of two screening procedures based on the location of their presentation.

- *Emergency department or COVID-specific clinic patients:* Initial pre-screening to determine study eligibility will necessarily proceed under waiver of informed consent and waiver of HIPAA authorization through the screening of electronic medical records by delegated members of the research team in participating emergency departments. Providers may contact study personnel to conduct pre-screening, as well. If the patient appears to be eligible based on pre-screening, and if acceptable to the treating physician, the patient will be approached by a study investigator or delegated study coordinator or research nurse to determine eligibility criteria. Patients seen in the emergency department but whose test results did not result prior to discharge will be given a study brochure with information to contact the study team if their test results positive and they wish to be considered for study participation. In addition, each site has clinical staff to call and alert patients regarding positive test results. These staff will alert the patient that they are eligible for a research study and that they may be contacted by study personnel, and will be given the opportunity to opt-out of this research contact. Once contact has been made, study personnel will conduct a screening questionnaire to determine eligibility criteria.

- *Drive-thru clinical patients:* M Health Fairview will have 4 drive thru centers for SARS-CoV-2 screening. Patients presenting to one of the centers will be given a brochure informing them that if they test positive and are interested in enrolling in a clinical trial of a new treatment for COVID-19 to contact our study coordinators (see attached study related materials). Once contact has been made, study personnel will conduct a screening questionnaire to determine eligibility criteria.
- *Dashboard:* In addition, participating sites have an electronic dashboard or electronic-medical record based report of all pending and confirmed positive COVID-19 tests that can be used for real-time prescreening of emergency department or COVID-clinic patients.

5.2 *Enrollment:* Patients or their legally authorized representative, with due consideration of vulnerable patient populations, (see section 9) will be eligible for consent by delegated members of the study team with appropriate training and experience in the conduct of human subjects research. Enrollment will similarly occur via one of two methods based on location of identification. **In all cases, consent converations will occur via telemedicine, institutionally approved video connection platform, or phone call (drive through patients or ED patients discharged prior to randomization) which limit traditional face-to-face contact.** If the participant regains capacity to consent, we will reconsent the participant in the study. If they decline, further study procedures will stop but previously collected data under the LAR consent will be utilized. If the participant does not regain capacity to consent, study procedures will continue under consent of the LAR.

- *Rationale for the use of telemedicine, video connection, or phone consent:* We have chosen this method of consent *in order to minimize risk to research team and healthcare providers, and to decrease community spread of the disease*. We have prior experience using telemedicine and phone consent coupled with electronic consent form review for time-sensitive clinical trials of stroke. While the *rationale* for eConsent is different in this case (minimization of disease spread during a pandemic), we believe it is *appropriate* for the disease and intervention being studied. LARs will not be used for remote consent. Critically, the low-dose and established safety profile of losartan, with multiple studies demonstrating minimal side effects on blood pressure in healthy patients[33-36] without an overactive renin-angiotensin-aldosterone system, combined with the close remote follow-up methods proposed in this study make the risk: benefit ratio for the alteration of traditional consent process acceptable for participants, providers, and the public.
- *Emergency department or COVID-clinic patients (patient is still in the emergency department or clinic):* For the sake of healthcare provider safety, and to minimize the spread of the virus, this visit will occur via a HIPAA compliant telemedicine consultation using tablets with telemedicine capabilities housed in the emergency department or with the study team. At this visit, consents will be reviewed in detail with the subject or LAR. The subject or LAR will have the opportunity to ask questions. If the patient (or LAR) agrees to become a study participant, electronic consent will be obtained using HIPAA and rule 11 compliant

electronic consent, stored and maintained in a secure RedCap server (see departmental policy on eConsent, attached).

- *Non-emergency department or COVID-clinic patients (patient returned home) or drive-thru clinic patients:* For the sake of healthcare provider safety, and to minimize the spread of the virus, pre-screening and consent will occur through a video connection or phone call. At this visit, consents will be reviewed in detail with the potential participant. The potential participant will have the opportunity to ask questions. If the participant agrees to become a study participant, electronic consent will be obtained using HIPAA and rule 11 compliant electronic consent, stored and maintained in a secure RedCap server (see departmental policy on eConsent).
- Eligible patients who meet inclusion criteria but do not have a documented creatinine and blood pressure reading within 7 days of the return of their positive COVID19 test results will undergo remote consent and enrolled. However, prior to randomization they will be required to participate in additional study screening at a clinic location prepared to accept known COVID-19 positive patients. The additional screening procedures will include: a blood pressure, creatinine, and potassium.

5.3 *Administration of study drug:* Patients will be given prepared components necessary for conduct of the study, including study drug (losartan or placebo), a thermometer, a home blood pressure cuff, and oropharyngeal swabs shipped supplies via same-day courier service.

5.4 *Patient follow-up:* Participants will receive phone calls by trained study personnel every other day for the 10 days of the intervention period to monitor for the development of complications including lowest daily blood pressure (measured at least once by home blood pressure cuff provided to the patient and medication compliance. Data will be documented into a Redcap database. The coordinators will have participants complete 2 qualitative surveys at enrollment, day 4, and day 10 (both attached in supplement). Surveys and adverse event assessments conducted within 1 day of the time point will be counted as qualifying and not considered missing. At day 15 (+/- 2 day), patients will be asked to return for repeat research blood draw to include creatinine testing. Patients will be contacted by phone at day 28 (+/- 3 days) and 90 (+/- 3 days) for short and intermediate term outcomes. If there is no follow-up due to lack of patient response, this will be documented and not counted as a protocol deviation.

5.5 Table of events:

		Study Day																
	*Screening / Enrollment**	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*28*	*90*
ELIGIBILITY																		
Covid-19 Result confirmation	X																	
Inclusion / Exclusion	X																	
Informed Consent	X																	
ADDITIONAL POST-ENROLLMENT PRESCREENING (IF NOT ALREADY AVAILABLE)																		
*Pregnancy assessment and birth control X plan***	X																	
Blood Pressure within 1 week of randomization	X																	
Creatinine / Potassium within 1 week of randomization	X																	
Randomize subject if eligible after additional prescreening	X																	
POST-RANDOMIZATION																		
Demographics	X																	
Medical History / CRF	X																	
*Dispense / administer study drug***	X	X	X	X	X	X	X	X	X	X	X							
STUDY PROCEDURES *(while outpatient)*#																		
Assessment of Hospitalization			X		X		X		X		X					X	X	
Adverse event assessment			X		X		X		X		X					X	X	
Review adherence			X		X		X		X		X							
Review and record blood pressures and temperatures			X		X		X		X		X							
PROMIS Survey					X						X						X	
Short Form 12 Health Survey					X						X						X	
Oropharyngeal swabs	X			X			X			X								
Potassium / Creatinine Check																X		
Follow-up biospecimens (OP swab + blood draw)																@		
Electronic medical record / death index review																		X

*Within 72 hours of + COVID-19 test results,

**In women of child-bearing age, patients must confirm negative test with study personnel prior to beginning treatment as well as confirmation of acceptable birth control method. For those capable of having children, a pregnancy test will be delivered to patients to confirm no pregnancy prior to initiation of study drug.

#Outpatient follow-ups +/- 1 day are accepted.

@ We will attempt to obtain oroopharygeal and blood biospecimens from patients hospitalized when they would otherwise have been planned

6.0 Data and Specimen Banking

6.1 Data management:

- *Storage and Access:* Data collection is the responsibility of the clinical research staff under the supervision of Drs. Tignanelli and Puskarich. Study data will be recorded within a RedCAP database with study personnel being granted access to the database based on the tasks listed in the Delegation of Authority log. Only deidentified data sets with all PHI removed will be shared for data analysis. The electronic consent (eConsent) forms, which will be maintained in a University of Minnesota RedCap database with established functionality for this purpose in our group. The database is HIPAA compliant.
- *Monitoring:* A monitor from Clinical Translational Science Institute (CTSI) or designated study monitor will review 100% of electronic consent documents, study drug administration data, and SAE reporting. Additionally, a random sampling of 5% of subjects will undergo full evaluation and comparison of source documentation with data entered into the study database. The first data monitoring visit will be scheduled once 10% of the cohort has been enrolled, with repeat monitoring after 50% and 100% of enrollments. Monitors will evaluate 100% of users to ensure assigned access is consistent with training and delegation of authority logs.
- *Release/Sharing:* Data will be shared among members of the study team with appropriate access assigned in Redcap based on study role, training, and delegation of authority. Data will be made available to assigned study monitors, the data safety monitoring board, the appropriate University of Minnesota oversight authorities, the Food and Drug Administration, and other state and federal regulatory authorities as required by state and federal law.
- *Data sharing:* Requests for data following study completion for sharing will be evaluated by a steering committee that will be established and will include the principal investigators. Requests will be evaluated on a case-by-case basis. If data are shared, only deidentified data will be shared.

6.2 Biospecimen management:

- *Specimen banking:* Biologic specimens (oropharyngeal swabs) provided by patients will be transported via courier service with the capacity to transport biologic materials with due consideration of communicable

diseases. Specimens will be transported and processed by the University of Minnesota BSL-3 laboratory and frozen at -80 C until the time of analysis. Samples will be deidentified and labeled only with a patient ID number.

- *Biospecimens and protocol deviations:* Baseline clinical laboratory results will be required to establish inclusion and exclusion criteria, and missing data will be reported as protocol deviations. However, significant barriers exist to the collection and processing of other biospecimens due to the increased containment required, meaning that not every study site may be able to accomplish these procedures. In addition, patient self-collection will lead to missing samples. While every effort will be made to obtain these biospecimens, failure to do so will not constitute protocol deviations.
- *Specimen sharing:* Requests for specimen sharing during or following study completion for sharing will be evaluated by a steering committee that will be established and will include the principal investigators. Requests will be evaluated on a case-by-case basis. If specimens are shared, human genetic analysis will only proceed on those patients who opt-in to genetic testing. Genetic testing of viral genomes will be allowed to proceed on all patients.

7.0 Sharing of Results with Participants

7.1 *Sharing of results:* Data collected within this study will be obtained from the participants themselves and recorded on collection templates or directly into Redcap, or will be obtained from the electronic medical record and thus are already available to the patient and treatment team. Any testing of biospecimens will occur at a later time point and do have specific clinical relevance and will not be shared with the patient.

7.2 *Sharing of genetic testing*

- *Disclosure of results:* There is no plan to disclose genetic results to the patients as none is yet planned.
- *If returning results to participants:* N/A

7.3 *Future analysis of genotypes:* Genetic testing, while potentially an area of future investigation as a means to determine if participants with specific genetic differences are more or less susceptible to COVID-19, is not currently planned nor funded. As such, data will not be disclosed to the participants. To the extent possible in future work, participants or families with rare variants will undergo attempts at anonymization.

8.0 Study Population

8.1 *Inclusion Criteria*

- Positive laboratory test for COVID-19 based on local laboratory standard
- Age greater than or equal to 18 years of age
- Upper respiratory symptoms (cough, rhinorrhea) *or* fever (>101.5)

8.2 *Rationale for inclusion criteria:* This is a pragmatic trial looking to enroll a diverse cohort of participants so the results may be broadly applicable to a wide patient population if efficacious. We do not have sufficient data to support lack of efficacy in a specific subgroup at this time to justify their exclusion. While we currently propose to exclude children due to insufficient time at the writing of this protocol to closely scrutinize safety and dosing in that group, along with logistical challenges of having different doses, we have plans to evaluate the possibility of expanding to include that patient population as soon as logistically feasible. Patients must be symptomatic to avoid enrolling asymptomatic carriers unlikely to meet the primary outcome.

8.3 *Exclusion Criteria*

- Randomization > 72 hours of meeting inclusion criteria
- Randomization > 7 days of symptom onset
- Currently taking an angiotensin converting enzyme inhibitor (ACEi) or Angiotensin receptor blocker (ARB)
- Prior reaction or intolerance to an ARB or ACE inhibitor, including but not limited to angioedema
- Pregnant or breastfeeding women
- Women able to have children not currently taking a protocol allowed version of contraception: intrauterine device, Depo-formulation of hormonal contraception (e.g. medroxyprogesterone acetate / Depo-Provera), subcutaneous contraceptive (e.g. Nexplanon), daily oral contraceptives with verbalized commitment to taking daily throughout the study, condom use or abstinence during the study. All women of child bearing age enrolled in this fashion will be informed of the teratogenic risks.
- Patient reported history or electronic medical record history of kidney disease, defined as:
    - Any history of dialysis
    - History of chronic kidney disease stage III or IV
    - Estimated Glomerular Filtration Rate (eGFR) of < 30ml/min/1.73 m^2 (must be have been measured within 1 month of enrollment)
    - Other kidney disease that in the opinion of the investigator, would affect losartan clearance
- Patient reported dehydration and significantly decreased urine output in the past 72 hours
- Most recent systolic blood pressure prior to enrollment <110 mmHg
- Patient reported history or electronic medical record history of severe liver disease, defined as:
    - Cirrhosis
    - History of hepatitis B or C

- Other liver disease that in the opinion of the investigator, would affect losartan clearance
- Documented AST or ALT > 3 times the upper limit of normal within 3 months of randomization (if available in electronic medical record)

- Potassium >5.0 mmol/L (must have been measured within 1 month) of enrollment
- Concurrent treatment with aliskiren
- Inability to obtain informed consent

8.4 Rationale for exclusion criteria: We expect treatment results to be available within 24 hours of sample collection related to delays in transport to a central facility. Coupled with delays in patient contact, 72 hours allows sufficient time for early outpatient intervention. Every effort will be made to minimize this window, however. Most patients will be hospitalized within 9 days of first symptoms, so patients with >7 days of symptoms have limited potential for benefit. Patients already taking or with prior adverse events to either an ACE inhibitor or ARB are excluded for risk of side effects. Losartan is a class D drug. Women of child bearing age (14-40) without a history of hysterectomy must have a documented negative pregnancy test in the emergency department or clinic in the past 7 days *or* have had a prior history of hysterectomy. Alternatively, if interested in the study, women of childbearing age will be sent a urine pregnancy test and report the result by verbal report over telemedicine or phone. Patients returning for prescreening labs and vital signs may have a serum pregnancy test performed, instead. If negative, they will be considered eligible. Given the class D pregnancy class, women of childbearing age must be taking a study-allowed form of contraception for the study period. Patients will have potassium and creatinine screening to decrease the risk of both kidney injury and decreased clearance. Patients on dialysis or with and eGFR <30 will be excluded, and 30-60 will have half-dosing. Patients with a documented potassium >5.0 will be excluded. Patients with hypotension will be excluded given an expected decrease of 6-8 mmHg in their blood pressure. Finally, all patients or their legally authorized representative will provide prospective written informed consent.

9.0 Vulnerable Populations

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

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from

	participation in the study.
Children	Excluded from Participation
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Included/Allowed to Participate
Non-English speakers	Included/Allowed to Participate
Those unable to read (illiterate)	Included/Allowed to Participate
Employees of the researcher	Included/Allowed to Participate
Students of the researcher	Included/Allowed to Participate
Undervalued or disenfranchised social group	Included/Allowed to Participate
Active members of the military (service members), DoD personnel (including civilian employees)	Included/Allowed to Participate
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Included/Allowed to Participate
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to Participate
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Included/Allowed to Participate
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

9.2 Additional safeguards:

- *Non-English speakers:* Excluding this group would compromise the principle of justice in clinical research. For groups likely to be enrolled given our known demographics (Spanish-speaking and Somali-speaking), we will translate informed consent forms (ICF) and use professional interpreters during both the consent and follow-up periods. These interpreters are available to our group during daytime hours by telephone. *We will request the use of the Short Form Consent for non-English speaking participants, and adhere to the regulations surrounding its use. When the translated ICsF become available, they will be used for non-English speakers.*
- *Employees or students of the researcher:* To minimize the potential for coercion, any employee or student of the research will undergo screening and informed consent by study personnel, but not by the investigator who is the direct supervisor of the vulnerable participant. The screening will not be performed by the study physicians or investigators, so this group may opt out in a deidentified fashion at that stage. Furthermore, if the potential participant wants to enroll, all interactions will occur with a different study investigator (such as the other co-principal investigator. These two clinical investigators work in different departments with different staff).
- *Undervalued or disenfranchised social group:* We will assure confidentiality, that they have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions.
- *Active members of the military (service members), DoD personnel (including civilian employees):* The status of participants of this group is not asked during the study nor known by study staff, and therefore vulnerability is not increased for anyone in this group.
- *Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare:* We will assure that information from participants in this study will be treated with the strictest confidentiality, that participants have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions.
- *Individual or group with a serious health condition for which there are no satisfactory standard treatments:* We will assure confidentiality, that they have the right to withdraw at any time without penalty, and they have the freedom to refuse to answer questions. We will also employ the teach-back method to ensure participants understand risks and demands of study participation.
- *Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior):* The status of participants from these groups is not asked during the study nor known by study staff, and that vulnerability is not increased for anyone in this group.

10.0 Local Number of participants

10.1 Locations: Enrollment will occur in the ED (or designated COVID19 areas) of MHealth Fairview Southdale Hospital, MHealth Ridges Hospital, University of Minnesota Medical Center East Bank and West Bank, Hennepin County Medical Center, Bethesda Hospital (COVID designated hospital, Mayo Clinic St. Mary's Hospital, or remotely via

the previously described methods for interested participants presenting to one of the 4 drive-thru clinics or stand-alone COVID clinic.

10.2 *Number of participants:* We will enroll 580 participants; this will provide adequate statistical power for testing our primary hypothesis and allows for 10% loss-to-follow-up.

11.0 Local Recruitment Methods

11.1 *Recruitment Process:* See section 5.0

11.2 *Identification of Potential Participants:* See section 5.0

11.3 *Recruitment materials:* Patients presenting to either the emergency department of the drive-thru clinic tested for COVID-19 will receive an informational brochure (attached as addendum) which provides information about testing, call-back, and the study. A phone number, email, and website will be created to allow participant to express interest in the study.

11.4 *Payment:* Patients will be eligible for a $25 gift card for their time to return for the 15-day blood draw for renal function testing.

12.0 Withdrawal of Participants

12.1 *Withdrawal Circumstances:* Participants may be withdrawn from research without their consent if they develop SAEs that the investigator believes to be likely related to the study drug. Participants may also be withdrawn from the study for repeated treatment non-adherence. Participants may also withdraw from the study at any time for any reason. All data from patients withdrawn from the study will be analyzed using intent to treat principles.

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

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

13.0 Risks to Participants

13.1 *Foreseeable Risks:* Potential risks of losartan are detailed in consent forms. The most severe risks of losartan use include teratogenicity in the setting of pregnancy, hypersensitivity including angioedema, symptomatic hypotension, worsening of renal function, and electrolyte abnormalities. The most common side effects of losartan include fatigue, weakness, diarrhea, chest pain and anemia. Subjects will be rigorously screened to ensure that they are at low risk for complications due to

losartan and they will be monitored closely for side effects and signs of toxicity. The package insert for Losartan has been included with this protocol. Clinical trial and post-marketing surveillance data (see package insert) demonstrate an excellent safety profile. In over 4,000 patients, there was a low incidence of adverse events (2.3%) comparable to placebo (3.7%). The effects more common in losartan than placebo were clinically minor, including dizziness (3% vs 2%), upper respiratory infection (8% vs 7%), nasal congestion (2% vs 1%) and back pain (2% vs 1%). While losartan has the potential to cause symptomatic hypotension, four studies have identified losartan has a negligible effect on resting blood pressure and heart rate in healthy volunteers.[34-37] It has been theorized there may be an increase risk of cardiac dysfunction in patients taking an ACE-I or ARB in COVID-19, though evidence for this effect is lacking. In fact, the most recent preprinted (non-peer reviewed) data from China now suggest a protective effect based on retrospective data compared to other antihypertensive regiments. However, this will be monitored carefully through admission rates and AE/SAE reporting to the DSMB, in addition to continuous monitoring of the primary outcome by the DSMB.

13.2 *Reproduction Risks:* Losartan is class D in pregnancy. Women of childbearing age will only be eligible for enrollment with a negative pregnancy test prior to enrollment. In addition, women breastfeeding will be excluded from the study.

13.3 *Risks to Others:* The primary risk to others is the risk to study personnel of becoming infected with COVID-19. To overcome this barrier, patients will be enrolled using an electronic consent process already established among our group for other studies. In addition, follow-up evaluations will preferentially be performed by phone. If a face-to-face evaluation or physical examination is required due to concern for adverse events, participants will be directed to a clinic or emergency department that is prepared for management of patients with COVID-19, and instructed on techniques to minimize exposure of others. Participants will generate potential biohazards (oropharyngeal swabs), the safety steps surrounding which are discussed in section 6.2.

14.0 Potential Benefits to Participants

14.1 *Potential Benefits:* If randomized to the intervention arm, and if losartan is demonstrated to prevent the progression of acute lung injury, patients may benefit by having reduced lung injury, decreased need for oxygen or mechanical ventilation, or possibly lower mortality. If randomized to the control arm, there is no direct potential benefit to the patient. However, the proposed research has the potential to significantly benefit people infected with COVID-19.

15.0 Statistical Considerations

15.1 *Data Analysis Plan:* All analysis will focus on comparisons between the treatment and control groups. Demographics and other baseline clinical characteristics will be summarized using descriptive statistics. Descriptive statistics will be presented by treat,emt group using mean, standard deviation, median, and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. The primary outcome, hospitalization at day 15, will be summarized by group using the sample proportion with 95% asymptotic confidence intervals. Treatment groups will be compared using the Chi-square test and the treatment

effect will be summarized by the absolute difference in the hospitalization rate between groups. Secondary endpoints will be summarized by the mean and standard deviation and compared using the two-sample unequal variance t-test, potentially after appropriate data transformations to assure that assumptions of the t-test are met. Time-to-event endpoints will be summarized by Kaplan-Meier curves and compared using Cox proportional hazards regression. For all endpoints, we will complete secondary analyses comparing for important baseline variables that are unequally distributed between treatment groups. Preplanned subgroup analyses are planned by age (dichotomized at 50 and by decade), history of hypertension, sex, and smoking history, timing of randomization from symptom onset, and respiratory support needed at the time of randomization. In addition, we will perform a preplanned pooled analysis with a planned national outpatient trial of losartan versus placebo targeting the same patient population with harmonized assessments and outcomes.

15.2 *Power Analysis:* Previously published literature from China suggest a 15% hospitalization rate for patients infected with coronavirus.[7,30] To detect a difference in hospital admission rate of 15% in control vs. 7% in the intervention group, with alpha of 0.05 and 80% power using a two-sided test, we will need 264 patients in each group. We will enroll a total of 290 patients in each group (total sample size of 580) to account for the possibility of 10% loss-to-follow-up.

15.3 *Data Integrity:* The principal investigator will manage oversight of quality control for collected data. Recruitment of subjects will be performed using inclusion/exclusion criteria defined above. Study data will be recorded within a RedCAP database, which is HIPAA compliant, password protected with variable assignable security access and an audit trail consistent with all regulatory requirements for maintenance of clinical trial data. Data summaries and quality control checks will be run routinely.

16.0 Health Information and Privacy Compliance

16.1 **Select which of the following is applicable to your research:**

☐My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

☒ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 **Identify the source of Private Health Information you will be using for your research (Check all that apply)**

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒I will collect information directly from research participants.

☐I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐I will retrieve record directly from axiUm / MiPACS

☐I will receive data from the Center for Medicare/Medicaid Services

☒I will receive a limited data set from another institution

☒Other. Describe: CTSI's BPIC will be used to pull structured data directly from EPIC into redcap (ED vitals, labs, etc.). HCMC will enter data into our Redcap research database. Study coordinators will contact patients daily to obtain data and will input it directly into the Redcap research database.

16.3 *Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed:* Study coordinators and BPIC will review if patients have opted out of research by using the opt-out flag within Epic to determine research status. Only patients that have opted-in to research or have expressed that they wish to delay opt-out status will be included in this study.

16.4 *Approximate number of records required for review:* 580, BPIC will be used to extract structured data, for unstructured data or patients that are not admitted to the hospital phone calls by study coordinators will collect data which will be manually entered into Redcap.

16.5 *Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes:*

☐This research involves record review only. There will be no communication with research participants.
☒Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.
☐Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

16.6 *Explain how the research team has legitimate access to patients/potential participants:* Informed consent will be obtained from patients granting access to clinical data for study participants.

16.7 *Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).*

☒In the data shelter of the Information Exchange (IE)

☒Store ☒Analyze ☒Share

☐In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐Store ☐Analyze ☐Share

☒In REDCap (recap.ahc.umn.edu)

☒Store ☒Analyze ☐Share

☐In Qualtrics (qualtrics.umn.edu)

☐Store ☐Analyze ☐Share

☐In OnCore (oncore.umn.edu)

☐Store ☐Analyze ☐Share

☐In the University's Box Secure Storage (box.umn.edu)

☐Store ☐Analyze ☒Share

☐In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐Store ☐Analyze ☐Share

☐In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐Store ☐Analyze ☐Share

☐Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smart device (iPhone or Android devices) that you have not already identified in the preceding questions

❒ will use a server not previously listed to collect/download research data

❒ will use a desktop or laptop not previously listed

❒ will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

❒ will use a mobile device such as an tablet or smartphone not previously listed

16.8 *Consultants. Vendors. Third Parties.* N/A

16.9 *Links to identifiable data:* All information that identifies study subjects will be handled in accordance with regulatory bodies including HIPAA regulations and the cIRB. This information will be made only available to the principal investigators and study personnel who directly participate in the research calls. Prior to enrollment, participants will sign an authorization to use and disclose PHI for research purposes. All staff will have been trained in the use of PHI. Subjects will be assigned a random subject ID number and a link between identifiers will be maintained in an excel log which will be stored in a secure folder in the AHC-IE

data shelter, the University of Minnesota's most secure healthcare research environment. Only the principal investigators and study nurses will have access to this file.

16.10 *Sharing of Data with Research Team Members:* A fully de-identified (of all PHI) database will be generated which will be used for statistical analysis and for monitoring by our DSMB. This database will exist within Redcap.

16.11 *Storage and Disposal of Paper Documents:* At this time we do not anticipate any paper documents related to this study. Everything, including consents will be done electronically. If the need for paper collection templates becomes evident, these documents will be stored in locked rooms where only study personnel have access. They will be maintained for 7 years as legally required, after which time they will either be destroyed or moved to long-term storage.

17.0 Confidentiality

17.1 *Data Security:* All data will be stored on servers (Redcap and CTSI AHC-IE data shelter) managed by the University of Minnesota IS. No data will be stored on individual research computers, flash drives, etc. These servers Redcap and the data shelter meet all data regulatory requirements and are HIPAA compliant.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 *Data Integrity Monitoring:* Data entry will be performed by trained members of the research team who have received documented delegation of authority. Data integrity will be overseen by the PIs. A monitor from Clinical Translational Science Institute (CTSI) will review 100% of electronic consent documents, study drug administration data, and SAE reporting. Additionally, a random sampling of 5% of subjects will undergo full evaluation and comparison of source documentation with data entered into the study database. The first data monitoring visit will be scheduled once 10% of the cohort has been enrolled, with repeat monitoring after 50% and 100% of enrollments. Monitors will evaluate 100% of users to ensure assigned access is consistent with training and delegation of authority logs. The project research coordinators at the sites will maintain binders containing pertinent documents and information including IRB approval letters, documentation of GCP training, licenses, human subjects research ethics training certificates, curriculum vitae, and correspondence.

18.2 *Adverse events reporting*

- *Definition of an Adverse Event (AE):* An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study but does not necessarily have a causal relationship with study agent/intervention or procedures. A clinical trial adverse event is defined as any untoward medical event associated with the use of a drug or study procedure. The Investigators will determine daily if any adverse events occur during the period from enrollment (signing of the informed consent) through study day 15. Investigators will determine if the event is serious or related to the study drug. The rationale for this time window is the half-life of 2 hours for losartan and 6-9 hours for its metabolite. Even in the setting of impaired clearance, 3 days after study drug cessation is more than adequate to help to define the period at risk from losartan. Abnormal

results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal,
- is associated with a serious adverse event (SAE),
- leads to additional treatment or to further diagnostic tests, or
- is considered by the Investigator to be of clinical significance.

- *Definition of a Serious Adverse Event*: Adverse events are classified as serious or non-serious. An SAE is any AE that is:
  - *Fatal,*
  - *life-threatening,*
  - *requires or prolongs a hospital stay,*
  - *results in persistent or significant disability or incapacity,*
  - *a congenital anomaly or birth defect, or*
  - *an important medical event.*

    Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent 1 of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. Serious adverse events will be collected during the first 15 study days, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

  Study site personnel must alert a study investigator of any serious and study drug or study procedure related adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form.

  All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

- *Preexisting Condition:* A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

- *Post-study Adverse Event:* All unresolved AEs will be followed by the Investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, study personnel will instruct each subject to report any subsequent event(s) within 3 months of study completion that the subject, or the subject’s

personal physician, believes might reasonably be related to participation in this study.

- *Abnormal Laboratory Values:* A clinical laboratory abnormality should be documented as an AE if any 1 of the following conditions is met:
    - The abnormality suggests a disease and/or organ toxicity that worsened from the time of enrollment, or
    - The abnormality is of a degree that requires active management; e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
- *Continuous SAEs of interest monitoring:* The following SAEs will be continuously reported to the DSMB: deaths, hospitalization, cardiovascular events (need for vasoactive drugs or fluids for hypotension), or respiratory events (worsening hypoxia, worsening acute respiratory distress syndrome, or new respiratory failure).
- *Other clinical Outcomes that may be exempt from adverse event reporting:* Study specific outcomes as outlined in 5.1 and 5.2 are exempt from adverse event reporting unless the investigator deems the event to be related to the study procedures (or of uncertain relationship) or if the event leads to discontinuation of study procedures. The following are examples of events that will be considered study specific clinical outcomes and will be systematically tracked through the study design. The rationale for this criteria is that adverse event reporting can be sporadic and inconsistent, so events more likely to be truly related to a study intervention are better treated by consistent tracking through the systemic design and collection of potentially related adverse events:
    - Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin.
    - Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine.
    - Hematologic/coagulation events: coagulopathy, disseminated intravascular coagulation, thrombocytopenia, or thrombocytosis.
    - Changes in serum sodium and potassium
- *Scales Used to Grade Severity of Adverse Events:* All AEs will be graded in the following manner:
    - Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the participant's daily activities.
    - Grade 2 (Moderate): Events result in a low level of inconvenience or concern. Moderate events may cause some interference with functioning.
    - Grade 3 (Severe): Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
    - Grade 4 (Life-threatening): Any adverse drug experience that places the participant, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death).
    - Grade 5 (Death)

- *Scales Used Attribute Adverse Events*: The Principal Investigator will assess the relationship of all AEs to any drug or study procedure:
    - Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
    - Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
    - Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.
    - Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study agent/intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
    - Not related: The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.
- *Anticipated Adverse Events*: Adverse events are not expected from any of the study procedures. We do not expect any serious adverse events due to losartan.
- *Recording and Documentation*
    - At each contact with the subject, personnel must seek information as to discomforts or adverse experiences by specific questioning and, as appropriate, by examination. This will typically occur via phone or telemedicine due to concerns regarding infectious

contagion. Information about AEs to be recorded includes event description, time of onset, investigator assessment of severity, relationship to Study Agent(s)/Intervention(s), and time of resolution/stabilization of the event. All AEs occurring during the study period (from time of consent signing to study day 15) must be documented appropriately regardless of relationship to study products or procedures unless included on the list of clinical outcomes that may be exempt from adverse outcomes reporting as part of the study protocol and outcomes. Information on all identified AEs will be recorded within 5 days recognition, while SAEs will be reported within 24 hours in the appropriate AE module of the case report form (CRF) on Redcap.

18.3 Data Safety Monitoring: A data safety monitoring board (DSMB) has been convened and includes 4 individuals meeting the key element criteria below, and includes a biostatistician with prior clinical trials DSMB experience. The DSMB will follow the guidance as outlined in the application and the attached charter unless there is a compelling, unanticipated reason to deviate from these rules. Data regarding the primary outcome (hospitalization) will be reported to the DSMB continuously, consistent with continuous study monitoring principles. The DSMB may recommend stopping the trial early only for safety, following these guidelines:

> [Patient Safety] A recommendation to suspend, alter the study, or stop for harm would occur if during continuous monitoring there is strong evidence that the rate of IRB-reported SAEs was significantly higher in the experimental group than in the placebo group. SAEs (including hospitalization, the primary SAE of interest) will be reported within 24 hours, allowing for continuous study monitoring. We will conduct formal interim analyses for safety at 5%, 10%, 15%, 20%, 30%, and 50% of enrollment. With a baseline event rate of 15%, this corresponds to formal analyses after every ~5 events initially, decreasing to every ~10 as data accumulates. Despite the lower number of formal preplanned analyses, the DSMB will still receive near *real-time reporting of hospitalizations* and *deaths*, and can deviate from this strategy and perform earlier testing if desired. They retain authority to change this plan if the continuous reporting suggests harm prior to the first formal planned assessment if they feel that a formal hypothesis test is warranted. In addition, the DSMB may request additional safety assessments after the 50% assessment, if they feel that additional formal testing is needed.

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

1. Expertise and independence: The members must have expertise in the area of study, not be study authors and have no financial conflict of interest.

2. Members will sign a confidentiality agreement.

3. It is preferred that the DSMB have a face-to-face initial meeting, but can meet by telephone thereafter more frequently.

4. All meetings must follow standard operating procedures (SOPs).

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

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 *Protecting Privacy:* Conversations will be held in a private room whenever possible. Telephone calls will be performed one on one. The electronic consent process takes place using a secure RedCAP server that is HIPAA compliant.

19.2 *Access to Participants:* Conduct of the study and determination of both safety and efficacy of the intervention requires access of the medical records. All study personnel undergo human subjects protection training and understand and value privacy standards set forth by HIPAA. Participants enrolled in the trial are made aware during the informed consent procedure that study personnel will be required to access this private information for trial conduct, and consent to this access prior to agreeing to participate.

20.0 Compensation for Research-Related Injury

20.1 *Compensation for Research-Related Injury:* There is no compensation available for research related injury.

20.2 *Contract Language:* N/A.

21.0 Consent Process

21.1 *Consent Process (when consent will be obtained):* All subjects participating in this study or their LARs will be required to provide prospective informed consent using an eConsent platform with an accompanying phone call or video feed to conduct the consent conversation. Prior to doing so, will discuss the study with study personnel who have been specially trained in obtaining informed consent. Our team has significant experience in this process, with due consideration of vulnerable patient populations. The subject or LAR will review the eConsent in detail and have the chance to ask questions. The personnel will then ask the subject questions to ensure that they understand the information presented in the consent discussion using a teach back method. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A copy of the informed consent document will be available electronically to the participants during the consent conversation and a signed copy will be emailed for their records. The participants may withdraw consent at any time throughout the course of the trial (see withdrawal procedures). The eConsent forms are included in this IRB submission.

21.2 *Waiver or Alteration of Consent Process (when consent will not be obtained):* N/A

21.3 *Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):* N/A

21.4 *Non-English Speaking Participants:* Spanish and Somali speaking persons, who represent the vast majority of non-English speaking patients in the study hospitals and clinics, will be included as described above.

21.5 *Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):* These patient groups will be excluded per the study protocol. If logistical and scientific concerns can be adequately addressed, we will submit a revised application with an ethical framework, scientific support, and logistical considerations.

21.6 *Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consents:* The enrollment of these patients will necessarily by affected by the location of presentation and timing of assessment. The identification of patients who lack consent capacity will not be possible in ED patients discharged or in patients presenting to drive-through clinics in this study since capacity assessments, such as the UBACC or the MacArthur Competence Assessment tool, are difficult to conduct over telemedicine or the phone, and methods of administering capacity screening tools in these settings have not yet been validating. Patients screened in the ED still physically present could be enrolled. To establish capacity in this setting, the MacArthur Competence Assessment tool will be administered by trained study personnel. If the patient lacks capacity, a LAR may provide consent for these participants on their behalf. For adults unable to consent, consent will be obtained from a legally authorized representative in the following order of priority consistent with Minnesota State Law: health care agent previously assigned via a health care power of attorney, spouse, parents, adult children, and then adult siblings. An incapacitated adult who has a court appointed guardian would require permission of the court for enrollment, and these participants will be excluded practically from the trial.

21.7 *Adults Unable to Consent:* These patients will be evaluated using the same process as *21.6*, and may be eligible for consent via an LAR if physically present in the ED.

21.8 *Assent and dissent in adults with fluctuating or limited mental capacity:*

- *Assent*: If patients might have capacity, we use the MacArthur Competence Assessment Tool for Clinical Research. If they do not reach the pre-specified threshold for capacity, we seek from an LAR. We do not seek further assent, as these patients are frequently intubated, delirious, or medically sedated
- *Dissent*: However, even if the LAR consents to the trial, if the patient is awake and alert, but dissent, we will exclude the patient.

22.0 Setting

22.1 *Research Sites:*

- *Emergency Departments*
  - M Health Fairview Ridges Hospital - Emergency Department
  - M Health Fairview Southdale Hospital - Emergency Department
  - M Health Fairview University of Minnesota - East Bank Emergency Department

- M Health Fairview University of Minnesota - West Bank Emergency Department
- M Health Fairview Clinics performing COVID testing
- Hennepin County Medical Center - Emergency Department
- Hennepin County Medical Center – Outpatient / COVID-Clinics
- North Memorial Hospital and Clinics
- Mayo Clinic – Emergency Department
- Mayo Clinic – Outpatient / COVID clinics

● M Health Fairview Drive through COVID-19 testing clinic sites

- Brooklyn Park Urgent Care
- Woodwinds Walk-in Clinic
- Maplewood Walk-in Clinic
- Oxboro Clinic Urgent Care

22.2 International Research: N/A

23.0 Multi-Site Research

23.1 Study-Wide Number of Participants: 580

23.2 Study-Wide Recruitment Methods: N/A

23.3 Study-Wide Recruitment Materials: Study brochures (attached) will be made available at all sites.

23.4 Communication Among Sites:

23.5 All sites have the most current version of the protocol, consent document(s), and, when applicable, HIPAA authorization.

● All required approvals (initial, continuing review, and modifications) have been obtained at each site (including by the site's IRB of record).

● All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.

● All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.

● All local site investigators conduct the study in accordance with applicable federal regulations and local laws.

● All non-compliance with the study protocol or applicable requirements will be reported in accordance with university or local policy.

● All other reportable events in accordance with university or local policy

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

24.0 Coordinating Center Research: N/A

25.0 Resources Available

25.1 ***Resources Available:*** It is difficult to estimate how many patients will develop COVID-19 in Minneapolis; however, given estimates from other countries it is likely to be 1000's if the virus is not contained.

The study PIs and research team will contribute at least 20% of their research time towards conducting and completing this study, we will leverage the rich resources of the UMN SIREN network hub and HCMC emergency department research infrastructure (of note, Dr. Puskarich is research director at HCMC, as well as associate research director at the University of Minnesota). In total across sites, this include >8 FTE of highly trained research nurses, coordinators, and research assistants across sites managed by the co-I plus an additional on-call pool of 8 additional trained associates providing 24/7 coverage for this and other studies. In addition, more personnel are available if funds are released for conduct of this study. All study members have completed all required responsible conduct in research coursework and have extensive research experience. The research team is built for mobile, multi-site enrollment in time-sensitive emergency care research, and has been a consistent top enroller in the NIH supported emergency care SIREN, StrokeNET, NETT, and PETAL clinical trial networks for years.

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