C O N F I D E N T I A L

CLINICAL TRIAL PROTOCOL

The Randomized Elimination or ProLongation of Angiotensin Converting Enzyme inhibitors and angiotensin receptor blockers in Coronavirus Disease 2019 (REPLACE COVID trial)

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1. SPECIFIC AIMS AND TRIAL OVERVIEW

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is associated with a high incidence of acute respiratory distress syndrome (ARDS) and death. Hypertension and cardiovascular disease are risk factors for death in COVID-19. Angiotensin converting enzyme 2 (ACE2), an important component of the renin-angiotensin system, serves as the binding site of SARS-CoV-2 and facilitates host cell entry in the lungs. In experimental models, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to increase ACE2 expression in several organs, potentially promoting viral cell invasion, although these findings are not consistent across studies. Alternatively, ACEIs and ARBs may actually improve mechanisms of host defense or hyperinflammation, ultimately reducing organ injury. Finally, ACEIs and ARBs may have direct renal, pulmonary and cardiac protective benefits in the setting of COVID-19. Therefore, it is unclear if ACEIs and ARBs may be beneficial or harmful in patients with COVID-19. Given the high prevalence of hypertension in the world, the high prevalence of ACEIs or ARBs in hypertension (>1/3), and the clinical equipoise regarding the continuation vs. discontinuation of ACEIs/ARBs in the setting of COVID, a randomized trial is urgently needed. The aim of this trial is to assess the clinical impact of continuation vs. discontinuation of ACE inhibitors and angiotensin receptor blockers on outcomes in patients hospitalized with COVID-19.

The **primary endpoint** of the trial will be a global rank score that ranks patient outcomes according to four factors: (1) time to death, (2) the number of days supported by invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), (3) the number of days supported on renal replacement therapy or pressor/inotropic therapy, and (4) a modified sequential Organ Failure Assessment (SOFA) score. The modified SOFA score will include the cardiac, respiratory, renal and coagulation domains of the SOFA score.

Secondary endpoints will include:
(1) All-cause death.
(2) Length of Hospital Stay.
(3) Length of ICU Stay, invasive mechanical ventilation or extracorporeal membrane oxygenation.
(4) The Area Under the Curve of the modified SOFA (AUC SOFA) from daily measurements, weighted to account for the shorter observation period among patients who die in-hospital.

Exploratory endpoints will include:
(1) ICU admission or respiratory Failure Requiring Mechanical Ventilation.
(2) Hypotension Requiring Vasopressors, inotropes or mechanical hemodynamic support (ventricular assist device or intra-aortic balloon pump).
(3) Number of 28-Day Ventilator-Free Days (invasive and non-invasive).
(4) Maximal change in NT-proBNP from baseline.
(5) Change in serum creatinine between randomization and discharge (or time of death).
(6) Acute kidney injury during hospitalization (defined as KDIGO Stage 2 or higher or initiation of renal replacement therapy)
(7) Proteinuria and hematuria (urinalysis)

All analyses will be performed on an intent-to-treat basis. In participants randomized to continuation of these drugs, clinicians will be encouraged to continue the randomized treatment

but will be allowed to change the dose of ACEI/ARB or discontinue these medications if compelling clinical reasons are identified (such as hypotension of acute kidney injury). In participants randomized to discontinuation, treating clinicians will be reminded to restart therapy prior to discharge for compelling indications (such as cardiomyopathy), with the ultimate decision being left at the clinician's discretion. Sensitivity analyses will be performed on a modified intent-to-treat basis, including only data obtained during the period of time in which participants remain on the randomized treatment strategy.

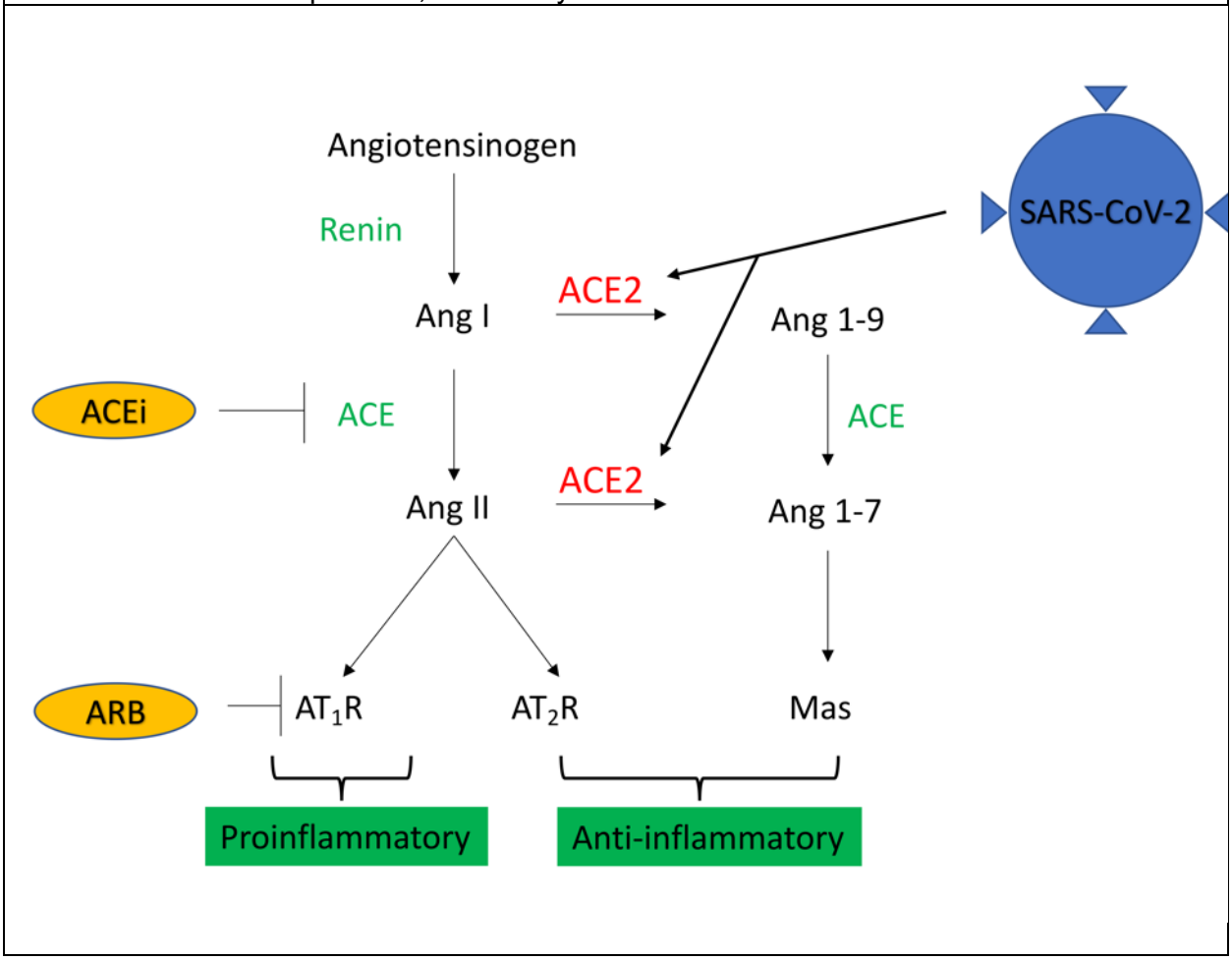
1. BACKGROUND AND SIGNIFICANCE

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is associated with a high incidence of acute respiratory distress syndrome (ARDS) and death.[1] Individuals infected with COVID-19 who developed ARDS and death have been characterized by older age and a higher prevalence of hypertension, diabetes, and cardiovascular diseases compared to those individuals with milder disease.[2-4] Several experimental studies suggest a mechanistic link between hypertension and SARS-CoV-2 severity. Given that over 800 million patients worldwide have hypertension,[5] it is imperative to identify potential interventions to reduce the risk of adverse outcomes in hypertensive patients with COVID-19.

Angiotensin converting enzyme 2 (ACE2), an important component of the renin-angiotensin system, serves as the binding site of SARS-CoV-2 and facilitates host cell entry in the lungs (**Figure**).[6,7] In experimental models, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been demonstrated to increase ACE2 expression in several organs.[8-11] This could lead to increased SARS-CoV-2 virulence in the lungs, increasing the risk of ARDS and death. However, these findings are not consistent across studies,[12,13] and have not been corroborated in humans.[14,15] Alternatively, ACEIs and ARBs may actually improve mechanisms of host defense or hyperinflammation, ultimately reducing organ injury and providing direct renal and cardiac protective benefits. Experimental data suggest a potential role for angiotensin receptor blockade in reducing adverse outcomes in SARS-Cov-induced lung injury.[16] Correspondingly, retrospective observational data in humans demonstrated lower rates of death and intubation in those patients who remained on ACEIs during hospitalizations for viral pneumonia from other viral pathogens.[17]

Thus, it is unclear if ACEIs and ARBs may be beneficial or harmful in patients with COVID-19. Given that over one-third of individuals with hypertension are prescribed ACEIs or ARBs,[18] it is critical to better understand the appropriate management of patients who present with COVID-19 who are already on these medications.

Figure. Interactions between SARS-CoV-2 and the renin-angiotensin-aldosterone system. ACE2 inhibits angiotensin (Ang) II activity in the renin-angiotensin system through degradation of Ang I and Ang II into Ang 1-9 and Ang 1-7. Ang II and the AT_1 receptor (AT_1R) have proinflammatory effects that may lead to acute lung injury or myocarditis, whereas the AT_2 and Mas receptors have anti-inflammatory effects. SARS-CoV-2 uses ACE2 as its functional receptor and induces acute lung injury and myocarditis through unknown mechanisms. ACEI and ARB inhibit the Ang II/AT_1R axis, which may be anti-inflammatory; they also increase ACE2 expression, which may increase SARS-CoV-2 virulence.



2. STUDY DESIGN AND POPULATION

3.1. Overview of study design

This will be a prospective randomized blinded end-point (PROBE) trial of continuation vs. discontinuation of ACEI/ARB therapy in patients admitted to the hospital for COVID-19.

3.2 Study Sites

The trial will be executed in the University of Pennsylvania Health System and various additional enrolling sites, When possible, enrollment at additional sites will undergo regulatory oversight via the SMART IRB mechanism. Enrollment sites that are not part of the SMART IRB Master Reliance Agreement will be required to obtain local IRB approval.

3.3. Study Population

We will enroll 152 subjects meeting the following criteria:

Inclusion Criteria

(1) Age 18 years or older
(2) Hospitalization with a suspected diagnosis of COVID-19, based on: (a) A compatible clinical presentation with a positive laboratory test for SARS-CoV-2, or (b) Considered by the primary team to be a Person Under Investigation due to undergo testing for COVID-19 in addition to compatible pulmonary infiltrates on chest x-ray (bilateral, interstitial or ground glass opacities).
(3) Use of ACEI or ARB as an outpatient prior to hospital admission.

Exclusion Criteria:

(1) Negative laboratory test for SARS-CoV-2 (a subset of these will include false negative patients, for whom timely confirmation with secondary testing will not be feasible)
(2) Systolic blood pressure <100 mmHg.
(3) Systolic blood pressure > 180 mmHg or >160 if unable to substitute ACEIs/ARBs for another antihypertensive class, per the investigator's discretion.
(4) Diastolic blood pressure > 110 mmHg
(5) Individuals with a history of heart failure in whom: (a) left ventricular systolic function is not known (no EF assessment available); (b) the EF is known to be <40% as per the last available 2D echo; (c) in whom the EF was >40% as per the last available echocardiogram but the there was a significant interim clinical event likely to be associated with a reduction in LV EF (such as an ST-elevation myocardial infarction or chemotherapy with cardiotoxic drugs), as per investigator's assessment.
(6) Serum K>5.0 mEq/L on admission.
(7) Known pregnancy or breastfeeding.
(8) eGFR <30 mL/min/1.73m^2
(9) ≥100% increase in creatinine (to a creatinine >2 mg/dl) compared to most recent creatinine in the past six months, if available
(10) Urine protein-to-creatitine ratio > 3 g/g or proteinuria > 3 g/24-hours within the past year
(11) Ongoing treatment with aliskiren or sacubitril-valsartan.
(12) Inability to obtain informed consent from patient.
(13) Inability to read and write or lack of access to a smart phone, computer or tablet device at the time of evaluation.
(14) Prisoners/incarcerated individuals

Participating in this protocol will not prevent participation in other COVID-19-related interventional or observational protocols.

3.4. Screening and enrollment

Trained clinical research coordinators will screen patients admitted to our health system using the electronic medical record. Inclusion and exclusion criteria will be reviewed to ensure participant

suitability. After participant eligibility is confirmed, electronic informed consent will be obtained from study participants using Institutional Review Board (IRB)-approved documents delivered via email. The clinician taking care of the patient will be informed about potential eligitibility. The patient will then be approached via phone, and the informed consent process will take place via telephone or video teleconference with one of the physicians in the study (regular phone call, Facetime or Skype, according to the participant's preference). Participants will be given the opportunity to have all questions regarding their participation answered.

Participants with suspected COVID who are not considered eligible for enrollment will be included in a retrospective and prospective registry which will be used for observational studies regarding the clinical course of this novel pathogen. Data regarding cardiovascular, renal and respiratory complications will be collected. **For the registry data collection only**, we will request a waiver for HIPAA authorization.

3.5. Randomized intervention

The randomized intervention will be the continuation of ACEI/ARBs at the doses previously prescribed for patients during their routine care vs. immediate discontinuation of these agents. All analyses will be performed on an intent-to-treat basis. Among participants randomized to continuation of these drugs, clinicians will be encouraged to continue the randomized treatment but will be allowed to change the dose of ACEI/ARB or discontinue these medications if any compelling clinical reasons are identified (such as hypotension, hyperkalemia, acute kidney injury). If an individual is on both ACEI and ARB therapy on admission (anticipated to be rare), that individual will be randomized to continuation of one or both medications (at the clinician's discretion) vs. discontinuation of *both* medications. In all participants randomized to discontinuation, treating clinicians will be reminded about the medication discontinuation upon discharge and will be prompted to consider reinitiation of the medication at that time if appropriate, per the clinician's discretion. All analyses will be performed on an intent-to-treat basis. Sensitivity analyses will be performed on a modified intent-to-treat basis, including only data obtained during the period of time in which participants remain on the randomized treatment strategy.

3.6. Randomization procedure

Following informed consent, participants will be randomized to one of the 2 treatment arms. A stratified blocked randomization with randomly permuted blocks will be performed based on site, sex, and age group, given the strong impact of these factors on outcomes in COVID-19. A sufficient number of complete blocks will be generated for each stratum so that randomized assignments are available for every eligible subject. Each block will contain an equal number of allocations to each arm. The randomization will be open with blinded end-point (PROBE trial). As soon as the patient is randomized, the study team will communicate the randomized treatment strategy to the primary clinician and any consultants in renal, cardiology, or pulmonary specialties who are involved in the patient's care. The investigator(s) performing endpoint adjudication will be blinded to the randomization arm, and will not be permitted to view provider notes.

3.7. Subject withdrawal / Early termination

Subjects may voluntarily withdraw from the study at any time and for any reason. The reason for study discontinuation will be recorded on the source documents and in all such subjects, we will document: (1) vital signs; (2) compliance with the treatment assignment; (3) Adverse effects. (4) Specific reason for withdrawal if possible.

3.8. Concomitant Medication

Subjects should be treated with standard of care medications for COVID-19 and associated comorbidities, at the clinician's discretion. Since all providers will be aware of the patient's ongoing medications, there is no risk of unrecognized drug interactions. Similarly, if a concomitant medication is felt to be necessary for the patient's care that would prompt a change in ACEI/ARB therapy, clinicians will be free to make the decision to deviate from the randomized therapy according to the patient's clinical needs.

3.10. Drug dispensing

Drug dispensing will be managed by the usual clinical mechanisms (clinical inpatient pharmacy rather than an Investigational Drug Pharmacy).

3.11. Biosample collection

Given the need to limit exposure between the patient and research staff, we will collect residual plasma available from clinical laboratory tests through the Department of Pathology and Laboratory Services. These samples will be utilized to assess proteomic and metabolomic biomarkers that may predict the response to our intervention or complications/outcomes from COVID-19. We will utilize only procedures for sample collection approved by Department of Pathology and Laboratory Services, which are currently being implemented to serve the need of investigators for COVID-19 clinical studies.

3.12. Telephone call 4 weeks after discharge

For participants who are discharged from the hospital, we will perform a telephone call approximately 4-weeks after discharge to document ongoing medications and to assess any adverse events that could take place after discharge. We will also assess quality of life using a brief validated standardized tool (Kansas City Cardiomyopathy questionnaire).

3. ENDPOINTS

The **primary endpoint** of the trial will be a global rank score, where the outcome of all patients in the trial are ranked from worst to best outcomes by increasing values of the following scoring system:

1) Days to In-hospital Death (Ordered Lowest to Highest)

Patient survives to discharge

2) Days on Invasive Mechanical Ventilation, VV ECMO, or VA ECMO (Ordered Highest to Lowest)

Patient does not require this support

3) Days on Renal Replacement Therapy or Inotropes/Pressors (Ordered Highest to Lowest)

Patient does not require this support

4) Area Under the Curve of the Modified SOFA Score (Ordered Highest to Lowest)

*ECMO = extracorporeal membrane oxygenation, which can be VV (venovenous) or VA (venoarterial)

The global rank score has several advantages compared to binary outcomes (e.g, all-cause death) or time-to-event outcomes (e.g., time to death).[19-21] It incorporates information about each of the highest-priority events in COVID-19, but allows these events to be prioritized. For instance, the principal outcome of interest is death, but even if there is no difference in rate of death, we would still be interested in a shorter duration of invasive respiratory support, and so on. This maximizes study power and minimizes the number of patients that need to be enrolled in order to identify clinically-meaningful differences.

The modified Sequential Organ Failure Assessment (SOFA) score will include the cardiac, respiratory, coagulation and renal domains of the SOFA score (appendix 1). The rationale for using a modified SOFA score (as opposed to the full SOFA score) as the last tier of the global rank score is as follows: (1) The cardiac, renal, respiratory and coagulation systems are the ones most likely impacted by our randomized intervention; [6-11,22-25] (2) These components can be easily and reliably adjuficated using electronic medical record review, thus avoiding any additional workload on the clinical team; (3) The nervous system (Glasgow comma scale) and liver (serum bilirubin) components of the SOFA score are not acquired daily on a routine basis in hospitalized patients in non-ICU settings.

Use of the modified SOFA allows all patients in the trial to be compared, even when no major adverse events occur.

Secondary endpoints will include:

1) All-cause death.
2) Length of Hospital Stay.

3) Length of ICU Stay, invasive mechanical ventilation or extracorporeal membrane oxygenation.
4) The Area Under the Curve of the modified SOFA (AUC SOFA) from daily measurements, weighted to account for the shorter observation period among patients who die in-hospital.

Exploratory endpoints will include:

1) ICU admission or respiratory Failure Requiring Mechanical Ventilation.
2) Hypotension requiring vasopressors, inotropes or mechanical hemodynamic support (ventricular assist device or intra-aortic balloon pump).
3) Number of 28-Day Ventilator-Free Days (invasive or non-invasive).
4) Maximal change in NT-proBNP from baseline.
5) Change in serum creatinine between randomization and discharge (or time of death).
6) Acute kidney injury during hospitalization (defined as KDIGO stage 2 or higher)[26]
7) Proteinuria and/or hematuria (urinalysis)

4. ADVERSE EVENTS

5.1. Adverse Event Reporting

The research team will keep a log of all adverse events that occur in the trial. The study team in charge of the conduct of the trial is up to date on all trainings pertaining to safety guidelines and adverse event reporting. In the context of COVID-19, the relatedness of adverse events is difficult to adjudicate, given the highly variable course of COVID-19 which may mimic the effects of ACEI continuation or withdrawal (for instance, hypotension or hypertension, worsening renal function, or cardiac decompensation). The study team will remain up to date with the literature regarding the clinical manifestations of COVID-19 in order to enhance the adjudication process in real time. All definitely related severe AEs will be reported within 48 hours to the IRB and the DSMB. In addition, the DSMB will examine data periodically in order to compare the incidence of adverse events in both arms.

5.2. Key definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug or biologic related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the pharmaceutical product.

5.3. Classification of AE/ADEs

A medically-qualified investigator must assess all AEs in terms of causal relationship to intervention, severity, and “expectedness” using the following guidelines.

Classification of Adverse Events for Causal Relationship to Study Interventions	
Not related	There is not a reasonable causal relationship to the investigational product and the adverse event
Unlikely related	No temporal association or the cause of the event has been identified, or the drug or device is unlikely to be implicated, but there is a low likelihood that a causal relationship exists.
Possibly related	There is reasonable evidence to suggest a causal relationship between the drug and adverse event.

Definitely Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

The severity will be classified as follows:

Classification of Adverse Events Regarding Severity Scale	
1	Mild AE. Awareness of sign, symptom, or event, but easily tolerated; no treatment required
2	Moderate AE. Discomfort enough to cause interference with usual activity and may warrant intervention. In the latter scenario, AE responds to treatment
3	Severe AE. Incapacitating, limiting usual/normal activities or significantly affects clinical status requiring hospitalization or prolongation of hospitalization.

Serious Adverse Events (SAE): An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes may occur:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or, more relevant for our trial, prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination is based on the opinion of either the investigators or DSMB (i.e., if any one of these believes it is serious, it must be considered serious).

Expectedness*:* The expectedness of an AE will be those that are reported to be associated with COVID-19 or anticipated from the pharmacological properties of the drug.

The following AEs are expected, disease-related events in patients with COVID-19

1. Arrhythmias, including sinus tachycardia, ventricular arrhythmias and atrial fibrillation
2. Acute coronary syndromes with or without coronary stenoses of coronary angiography
3. Myocarditis or worsening cardiac function
4. Shortness of breath, pneumonia, acute respiratory distress syndrome and respitatory failure
5. Fever
6. Leukopenia or leukocytosis, thrombocytopenia
7. Worsening renal (resulting in worsening electrolyte abnormalities, including hyperkalemia) and liver function
8. Worsening cognitive function

9. Coagulopathy, thrombosis, embolus, or limb ischemia
10. Hypotension or hypertension
11. Diarrhea, nausea, or vomiting
12. Anosmia (loss of sense of smell), which has been reported to occur with COVID-19.
13.

5.4. Pregnancy:

Angiotensin-converting enzyme (ACE) inhibitors are considered contraindicated during the second and third trimesters of pregnancy because of increased risk of fetal renal damage. First-trimester use, however, has not been linked to adverse fetal outcomes.[27,28] Therefore, known pregnancy will be an exclusion criterion for enrollment. In addition, females of reproductive age will undergo a pregnancy test which is required in standard clinical practice. The study team will remind clinicians for the need for this test if not already obtained. A positive test will prompt discontinuation from the study, since it may prompt changes in ACEI or ARB therapy by the treating clinicians based on conditions other than the COVID-19 clinical course.

5. DATA COLLECTION

A data coordinating center (DCC) will be established under the direction of Dr. Jordana Cohen. The DCC will oversee randomization, data entry, and DSMB meetings. The data for this trial will be collected in *ad hoc* source electronic case report forms. The informed consent will be electronic, and therefore all source documents collected in this trial will be electronic and housed in a secure UPHS or SOM server. This will allow efficient workflows regardless of location, quarantine, and social distance policies, since investigators and research staff can access these documents using existing secure VPN mechanisms. Data capture and storage will be accomplished within the framework of the Research Electronic Data Capture (REDCap) project. REDCap is a secure, web-based application designed exclusively to support data capture for research studies. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS and STATA, and procedures for importing data from external sources.

6. DATA SAFETY MONITORING BOARD

A DSMB will be assembled to provide independent oversight of the project. The DSMB will be responsible for assessing: 1) baseline comparability between groups; 2) participant accrual rate and retention; 3) data quality with special emphasis on eligibility data; and 4) patient safety. The board will make recommendations regarding: study continuation, protocol modification, and review of additional data. The conference call meetings and progress reports will be set by the DSMB. The DSMB will review detailed safety data according to pre-defined milestones (i.e., after 10 deaths or after the first 25% of participants are enrolled, whichever is first) which can be adapted as the trial proceeds, as per DSMB member decision.

7. STATISTICAL CONSIDERATIONS

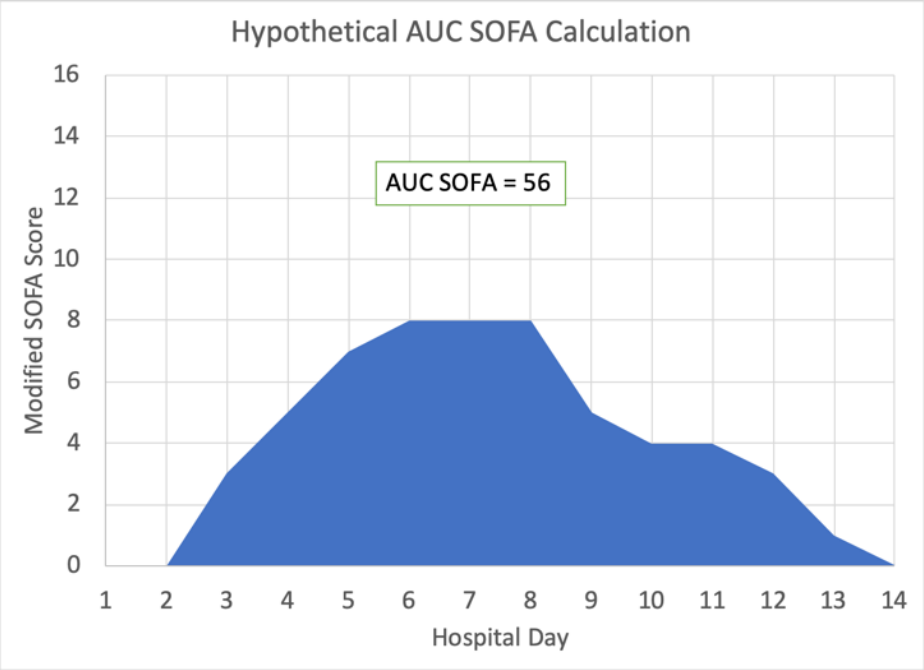
7.1. Power calculations

We will enroll until we have 152 participants with confirmed COVID-19. We anticipate that we will have to approach approximately 225 potentially eligible subjects to achieve this goal. Participants will be randomized to one of 2 interventions, continuation vs. discontinuation of ACEI vs. ARB therapy. Assuming feasible distributions of patients across each of the four hierarchies from the available published evidence,[2,29,30] we performed 10,000 simulations of

rank distributions of 152 patients, and determined that there will be 82% power at an alpha of 0.0471 (allowing for interim analyses after we have reached 50% and 75% of enrollment[31,32]) to observe a significant difference between the treatment arms. We also performed 10,000 simulations of rank distributions using a sample size of 200 patients (optimal size with the addition of more sites), and determined that there will be 92% power at an alpha of 0.0471. With regard to secondary endpoints, we will have 90% power to detect a 2 day difference in length of ICU stay and length of hospital stay assuming a standard deviation of 2[30] based on data from initial reports of these outcomes in China.[2,29] Power calculations were performed using python and PASS16.[33]

7.2. Data Analysis Plan

In order to summarize the SOFA score over the course of the hospitalization, we will calculate the Area Under the Curve of the modified SOFA (AUC SOFA) from daily measurements. The AUC SOFA will be ranked from highest to lowest so that lower ranks represent worse outcomes in alignment with the rest of the global rank score. The AUC SOFA is calculated as the area under the curve of daily modified SOFA values as in this hypothetical example:



The primary outcome variable will be the global rank score, a nonparametric ranked outcome. This approach has been used in several similar randomized controlled trials to facilitate evaluation of composite outcomes of binary and continuous findings accounting for censorship for death.[19-21] The predictor of interest for all aims will be intervention (continuation vs. discontinuation of ACEI/ARB therapy), with analyses based upon the total number of subjects randomized. Initial descriptive estimates of all measures will be generated for study participants by treatment group. Statistics will include estimates of central tendency, measures of variability, and derived moments of skewness and kurtosis. Analyses of distributional properties will be performed to determine if variance stabilizing or normalizing transformations should be applied. Outliers will be assessed via visual inspection of distributions and checked for accuracy. Additionally, the intervention groups will be compared using Fisher's Exact tests.

An initial assessment of the treatment effect will be performed using the the non-parametric Wilcoxon rank sum test. This will be followed by a more comprehensive linear regression analysis allowing for assessments of the treatment effect on each continuous outcome of interest while controlling for effects of other covariates including age, sex, ethnicity, history of pre-existing heart failure, history of pre-existing chronic lung disease, and ACEI vs. ARB therapy at baseline. For non-normal distributed outcomes, we will utilize non-parametric methods or consider distribution-stabilizing transformations. Levine's tests will be used to assess homogeneity of variance. The models will include data from dropouts.[34-36] Model assumptions will be examined (eg,QQ plots to assess normally distributed residuals for valid Wald tests). Secondary and exploratory outcomes of repeated measures will be evaluated using linear mixed-effects model analysis[37] allowing for assessments of the treatment effect on each continuous outcome of interest while controlling for effects of prespecified covariates, and a random subject effect. Secondary and exploratory time-to-event outcomes will be evaluated using Cox proportional hazards models. The proportional hazards assumption will be assessed via weighted versions of Kaplan–Meier curves using log–log plots and graphical displays based on the Schoenfeld and scaled Schoenfeld residuals and violations of the proportional hazards assumption will be addressed with a time-interaction term.[38]

We will make every possible effort to minimize missing data and ensure final assessments for participants opting to discontinue study participation. Missing data, however, is an inevitable problem in a longitudinal study. The mechanism for missingness-missing completely at random (MCAR), missing at random (MAR), nonignorable or not missing at random (NMAR)-will be evaluated prior to implementing methodology intended to minimize bias from missing data.[39] We anticipate that <5% of randomized subjects will have missing data in the components required to compute the study outcomes. Imputation procedures will be applied as needed for missing data.

The intent-to-treat principle of including all randomized participants in the outcome models will be followed. Analytic methods described above will take advantage of all available data. The possibility of systematic bias in the outcomes for those who withdraw exists. In participants randomized to continuation of these drugs, clinicians will be encouraged to continue the randomized treatment but will be allowed to change the dose of ACEI/ARB or discontinue these medications if compelling clinical reasons are identified (such as hypotension, hyperkalemia, or acute kidney injury). In participants randomized to discontinuation, treating clinicians will be reminded about the medication discontinuation upon discharge and will be prompted to consider reinitiation of the medication at that time if appropriate, per the clinician's discretion. Sensitivity analyses will be performed on a modified intent-to-treat basis, including only data obtained during the period of time in which participants remain on the randomized treatment strategy.

7.3. Subgroup analyses and effect modification

We will assess for effect modification and exploratory subgroup analyses will be performed according to sex, age,[40] race,[41] presence of pre-existing heart failure or left ventricular dysfunction, presence vs. absence of pre-existing chronic kidney disease, baseline ACEI vs. ARB,[42] and BMI.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Potential benefits of the proposed research, importance of the knowledge to be gained, and risk/benefit ratio

Potential benefits: There are no anticipated direct benefits to the subjects as a result of their participation in this study nor will this be implied when obtaining consent.

Importance of the knowledge to be gained: Our study will address a highly important clinical question that will impact the care of a large number of patients affected by the COVID pandemic. This study will provide randomized trial evidence about the impact of a specific initial course of action regarding the continuation vs. discontinuation of ACEIs/ARBs.
Risk/benefit ratio: given the importance of knowledge to be gained, the risk/benefit ratio of our trial is favorable.

8.2. Risks to study subjects

All subjects will be adults able to give informed consent. Subjects will be enrolled regardless of sex, race or ethnicity, aiming to assure adequate representation of women and African Americans. Children will not be enrolled. The risks to study subjects are related to the clinical equipoise itself: it is possible that one strategy is better than the other, but at the moment this clinical equipoise is not solvable based on clinical grounds or intuition. Furthermore, after the initial randomized strategy, our trial allows for altering the course of therapy based on clinical grounds that clearly favor one strategy based on clinical assessment as per the treating clinician (such as hypotension, which would prompt discontinuation of ACEIs/ARBs among patients randomized to continued therapy, or pre-discharge reinitiation fo these medications for compelling indications, particularly ACEIs in the setting of heart failure with a reduced ejection fraction).

The risk of short term ACEI or ARB withdrawal is generally minimal. Even in higher risk groups, such as patients with moderately decompensated heart failure (NYHA class II to III), heart failure decompensation is not observed until 4-6 weeks following ACEI/ARB withdrawal.[43] This time course far exceeds the typical duration of COVID-19 hospitalization. However, to ensure an even higher safety threshold, we created an additional exclusion criteria for any patients with left ventricular ejection fractions < 40%. Patients with heart failure and moderately reduced ejection fraction (EF 40-50%) should be even less likely to decompensate from ACEI/ARB withdrawal. Furthermore, we will remind treating clinicians of the potential need for reinitiation prior to hospital discharge, once the patient is stable for discharge from the COVID-19 standpoint. In patients without heart failure, including those with resistant hypertension, short term withdrawal of anti-hypertensives is safe and well-tolerated.[44] To ensure an additional margin of safety for this group, we created an additional exclusion criteria for patients with a baseline systolic blood pressure >180 mmHg or >160 if unable to substitute ACEIs/ARBs for another antihypertensive class, and for diastolic blood pressure ≥110 mmHg.

8.3. Adequacy of Protection Against Risks

8.3.1. Recruitment and Informed Consent:
Electronic informed consent will be obtained from the subjects prior to entry into the research study. Potential subjects will receive the IRB approved informed consent form electronically via email. We will use DocuSign, RedCap (consent document attestation) or other University of Pennsylvania Office of Clinical Research e-consent approved methods, to document subjects' willingness to participate in the research study. The principal investigator or sub-investigators will conduct the informed consent process via phone or video conferencing programs such as Skype which maximizes the efficiency of workflow and minimizes exposure of the research staff to SARS-CoV-2. The study intervention and potential associated risks will be explained to study subjects and they will have adequate time to ask questions. No study interventions will be initiated until the study team receives either the signed informed consent form or attestation documenting the subjects' agreement to participate. Subjects will either receive a copy of the signed document via email or a RedCap attestation verification email once they agree to participate.

8.3.2 Measures to minimize the risk of breach in confidentiality: All records will be treated with strict confidentiality according to HIPAA guidelines (all study personnel are trained on HIPAA regulations). We recognize that HIPAA provisions have been relaxed during the COVID-19 epidemic. However, all our eCRFs will be contained in HIPAA-compliant secure hard drives that sit behind the UPHS firewall. In the context of relaxed reagulations, we will continue to aim for strict confidentiality of patient data to the full extent possible. A secure database of patient information will be maintained. All documents for this trial will be electronic, but any unanticipated paper files that contain protected health information will be saved under lock in a secure area.

9. REGULATORY STANDARDS

The study will be submitted to the Penn IRB for approval. During the study, any amendment or modification to the protocol will be sent to the IRB. Protocol deviations will be handled according to Institutional guidelines.

Given that this trial is not aimed at obtaining regulatory approval of a novel drug, a labeled approved indication or repurposing of existing drugs, this trial does not require an FDA IND. This determination was made formally by the IND support unit at the University of Pennsylvania Office of Research Services.

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10. APPENDIX 1. MODIFIED SOFA SCORE

Variable	Points
SpO_2/FiO_2[45]	
≥ 400	0
315-399	+1
235-314	+2
150-235 and mechanically ventilated	+3
< 150 and mechanically ventilated	+4
Platelets, x 10^3/µL	
≥ 150	0
100-150	+1
50-99	+2
20-49	+3
<20	+4
Mean arterial pressure OR administration of vasoactive agents required (listed doses are in units of mcg/kg/min)	
No hypotension	0
MAP < 70 mmHg	+1
DOPamine ≤5 or DOBUTamine (any dose)	+2
DOPamine >5, EPINEPHrine ≤ 0.1, or nor EPINEPHrine ≤0.1	+3
DOPamine >15, EPINEPHrine > 0.1, or nor EPINEPHrine >0.1	+4
Creatinine, mg/dL (or urine output)	
<1.2	0
1.2-1.9	+1
2.0-3.4	+2
3.5-4.9 or UOP < 500 mL/day	+3
≥5.0 or UOP < 200 mL/day	+4
Maximum Total Score	16

11. APPENDIX 2. SCHEDULE OF EVENTS

Screening	Approach Team	Enrollment and Randomization	Monitor Clinical Data via EMR	Follow-up Phone Call
Date Diagnosis Confirmed or Suspected by Primary Team	→	→	After Randomization Until Discharge	4 weeks after discharge