A Randomized Phase II **T**rial of **H**ydroxychloroquine **I**n **C**ovid-19 **K**inetics (THICK)

Principal Investigator:	William Richards, M.D**.**
Sub Investigators:	Paul Rider, M.D
Data and Safety Monitors:	John Vandewaa M.D. Eduardo Calderon M.D.
Project Manager:	Winona Blount, RN, MSN
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CONFIDENTIALITYSTATEMENT

This document is confidential and to be distributed for review only to investigators, potential investigators, consultants, study staff, and the applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from the University of South Alabama, William Richards, MD unless it is necessary to obtain informed consent from potential study participants.

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Introduction:

A recent review of Hydroxychloroquine (HCQ) use for Cvovid-19 infections concludes: *"There is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice for other indications to justify clinical research on the topic."* [1]

Background:

HCQ, which is a less toxic derivative of chloroquine (CQ), has been shown to be effective in inhibiting Covid-19 infection in vitro. CQ and HCQ increase the pH of acidic intracellular organelles such as endosomes/lysosomes essential for membrane fusion, which inhibits Covid-19 entry into the cell. [2] [3]

HCQ is FDA approved for treatment of Rheumatoid arthritis and lupus erythematosus. Oral absorption of HCQ in humans is very efficient. Furthermore, a safe dosage 6 to 6.5 mg/kg/day of HCQ has been shown to generate serum levels of 1.4-1.5 micromolar in humans. Therefore, a safe oral dosage of HCQ will reach concentrations in tissues (liver spleen kidney and lung) that should inhibit Covid-19 infection. [3] Indeed, a French study demonstrated mean HCQ serum concentration of 0.46 micrograms/ml + 0.2 in human subjects receiving HCQ standard doses for treatment of Covid-19. [4]

Much of the Chinese experience with Chloroquine comes from a letter to the editor and a news briefing/conference held on February 15, 2020. The letter describes experience with more than 100 patients treated with CQ in multicenter clinical trials. The authors claim "Chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion and shortening the disease course". The letter provides no quantitative data to back their claims. [2] Another Chinese study demonstrated both HCQ and CQ have in vitro antiviral activity and anti-inflammatory effects but the HCQ is preferred because of its much better safety profile. They tested dosing schedule similar to that proposed herein and projected it would achieve effective treatment effects while preserving a good safety profile. These authors emphasize the need for a loading dose of HCQ to achieve faster clinical effect. [5]

At least one non-randomized clinical trial has been performed in France. [4] Covid-19 infected patients received 10 days of 600 mg of HCQ daily (divided doses of 200mg) with viral loads from nasopharyngeal swabs tested daily. Patients who deteriorated received Azithromycin AZ at a dose of 500 mg on day 1 and 250 mg/day for 4 successive days. Untreated patients from another hospital and inpatients who refused to be enrolled in the experimental protocol were used as negative controls.

	Day 3 post inclusion % of negative PCR	Day 6 post inclusion % of negative PCR
Controls N=16	1/16 = 6.3%	2/16 = 12.5%
HCQ N=14	5/14 = 35.7% ^	8/14 = 57.1% *

The subjects receiving HCQ were much more likely (P<0.02) to clear their viral load than subjects who did not receive HCQ. This limited study had many flaws and should be corroborated with randomized, blinded trials to either confirm or refute the efficacy of HCQ is early treatment of Covid19 infection to ameliorate disease severity, and reduce viral load.

Anticipated dates of study: March 27, 2020 – December 1, 2020

Hypothesis:

Oral Hydroxychloroquine taken in PCR positive patients/or health care workers with high suspicion of disease presence will increase the number of PCR negative patients, 7 days after initiation of therapy compared to control patients receiving placebo.

Study design:

ARM	Intervention
A: Experimental/Hydroxychloroquine	Hydroxychloroquine 200mg tablets 800mg orally once, then 600mg orally 6 - 8hours after first dose, then 200mg 3 times per day for 4 consecutive days
B: Control Placebo	Placebo 4 placebo tablets once, followed in 6 to 8 hours by 3 tablets, then 3 tablets 3 times per day for 4 consecutive days

Inclusion Criteria

- Symptoms occurring within 3 days prior to patient presenting to USA Facility for PCR nasopharyngeal swab
- Nasopharyngeal swab positive for Covid-19 infection and/or exposure and/or symptoms congruent with fever and cough
- Male or Female age 19 to 89 years
- Able to take oral medications
- Patients not requiring hospitalization

- Provision of informed consent

Exclusion Criteria:

- **Known history of EKG QTc prolongation abnormality**
- Contraindication or allergy to hydroxychloroquine
- Retinal eye disease
- Known glucose-6 phosphate dehydrogenase (G-6-PD) deficiency
- Known chronic kidney disease, stage 4 or 5 or receiving dialysis
- Weight < 40 kg
- Current use of: hydroxychloroquine or cardiac medicines of: flecainide, Tambocor; amiodarone, Cordarone, Pacerone; digoxin or Digox, Digitek, Lanoxin; procainamide or Procan, Procanbid, propafenone, Rythmal)
- Known hepatic disease (cirrhosis, hepatitis)
- Active treatment for cancer (chemotherapy, radiation, surgery within 3 months
- On immunosuppressive drugs steroids, antirejection medications.
- Recipient of solid organ transplant
- Pregnancy/breastfeeding
- Past medical history Porphyria (may exacerbate disease)
- PMH Psoariasis (can worsen disease)
- No access to internet or email
- Current suicidal thoughts according to Columbia scale
- In the screening process before signing consent, subjects will be asked if they are suicidal. If this response is yes, patients will be excluded from trial and directed to the National Suicide Prevention Lifeline: 1-800-273-8255.

Primary Outcome Measures:

1. NP swab viral load COVID19 Disease % of negative PCR NP swabs [Time Frame: 7 days]

2. Ordinal Scale of COVID19 Disease Severity [Time Frame: 6 days]

Participants will self-report disease severity status as one of the following 5 options; no COVID19 illness (score of 1), COVID19 symptoms present according to USA Health screening tool (score of 2), COVID19 symptoms present according to USA Health screening tool with hospitalization (score of 3), or COVID19 symptoms present according to USA Health screening tool with subject hospitalization and ICU care (score of 4), or COVID19 with death (score of 5). Increased scale score indicates greater disease severity.

Outcome is reported as the percent of participants who fall into each category per arm.

Secondary Outcome Measures:

1. Incidence of Hospitalization [Time Frame: 14 days]

Outcome reported as the number of participants in each arm who require hospitalization for COVID19-related disease.

2. Incidence of Death [Time Frame: 90 days]

   Outcome reported as the number of participants in each arm who expire due to COVID-19-related disease.

3. Incidence of Confirmed SARS-CoV-2 Detection [Time Frame: 14 days]

   Outcome reported as the number of participants in each arm who have confirmed SARS-CoV-2 infection.

4. Incidence of Symptoms Compatible with COVID19 (possible disease) [Time Frame: 90 days]

   Outcome reported as the number of participants in each arm who self-report symptoms compatible with COVID19 infection.

5. Incidence of All-Cause Study Medicine Discontinuation or Withdrawal [Time Frame: 14 days]

   Outcome reported as the number of participants in each arm who discontinue or withdraw medication use for any reason.

6. Immunity to Covid-19 [Time frame: 6 ± 2 weeks]

   Blood tests to determine level of immunity in each subject

Power analysis:

Full enrollment in the study will occur when 58 subjects are enrolled into the study.

Information used: From the Gautret study [4] the following estimates are available:
Proportion of negative PCRs on day 6 in HCQ treated patients = 0.571
Proportion of negative PCRs on day 6 in patients from control group = 0.125
That is the difference of 0.446 was observed in two group proportions.

Power analysis: Using 5% type I error rate and 80% or 85% power to estimate the difference of 0.40, 0.45, 0.50 (i.e. 40%, 45%, 50%) in the proportion of negative PCRs in two groups (treatment and control) the following sample sizes are needed from each group.

Difference to estimate	Power = 0.80	Power = 0.85
0.40	**19**	22
0.45	15	17
0.50	12	14

We will use a difference to estimate of 0.4 and a power calculation of 0.80, which indicates 19 patients in each arm needed to achieve a 5% type I error rate.

A significant limitation of the study is our current turnaround on the PCR nasopharyngeal swab test which is 96 hours awaiting test results. It is important to start the healthcare workers with significant exposure and with symptoms started on medication; before they deteriorate, therefore we will enroll some patients without actual confirmation of a positive PCR test. We anticipate that testing using an in house USA clinical pathology test will be available within 2-4 weeks and provide 6-hour turn around. Until that, time we estimate 25% of health care workers who have an exposure and symptoms will have a negative PCR. Therefore, we will increase the number of subjects in each arm of the study in order to account for ineligibility or who dropout from the studies. We estimate 25% of subjects enrolled in the study will not return for day 6 nasopharyngeal swab. Patients may be feeling so well that they decline to return or they are hospitalized at a non-USA hospital and unable to obtain a swab on day 6. The number needed in each group will be increased by 50% to ensure that we have 19 patients in each group (N=29 each group) to ensure that the study is adequately powered.

Fisher's test will be used to compare proportions from two groups.

Study Procedures

Schedule of Events					
	Pre- Treatment Period	**Day 6**	**Day 7**	**Day 30**	**End of Study 6 Weeks**
Consent	**X**				
PCR NP Swab St	**X**				
Inclusion/Exclusion	**X**				
Medical History	**X**				
Severity Of Symptom Survey	**X**	**X**		**X**	
Repeat PCR NP Swab			**X**		
Lab Draw for immunology studies					**X**

Consent Process

1. Informed Consent will be thoroughly explained over the phone. Consent will then be emailed to subject. If the subject is an employee, subject will return consent via their employee email. If the subject is a non-employee, the subject will sign his or her informed consent in person before any trial related processes are to begin. To reduce transmission of Covid-19 we will also be utilizing other options- see options 2 and 3.

2. To avoid transmission of Covid-19, it is preferable by the PI and best practice that a physical paper consent be eliminated. As an alternative to paper, the subject will sign his or her informed consent via Redcap, which will deliver an unsigned informed consent to the subject through email and signed consent back to Research Clinical Coordinator through email. Subject will be verified via photo ID upon arrival at testing site on Day 1 before any trial related processes begin or medication is dispensed.

3. In the event we are not able to utilize Redcap or email- the subject will give verbal consent to two Research Clinical Coordinators over the phone to avoid a physical paper consent, thereby avoiding transmission of Covid-19. The signatures of both Research Clinical Coordinators who receive verbal consent from subject will suffice/replace subject's physical signature. Reason patient is unable to sign should be documented as prevention of transmission of Covid-19. Subject will be verified via photo ID upon arrival at testing site on Day 1 +/- 1day before any trial related processes begin or medication is dispensed.

Randomization:

Double Blind Randomization will be allocated 1:1 between placebo and Hydroxychloroquine arms. Dr. Madhuri Mulekar, Chair of Mathematics and Statistics at the University of South Alabama, will create randomization schedule. Chronological patient IDs will be provided to the MCI outpatient pharmacy. Brittney Carden, PharmD will be responsible for opening the randomization assignment and dispensing the appropriate drug (hydroxychloroquine or placebo). All parties are to remain blinded except Brittney Carden, PharmD

Treatment Schedule:

Subjects will be randomized to Arm A or B

ARM A: Experimental Arm

- Enrolled subjects randomized to experimental arm (Arm A), will receive the study drug hydroxychloroquine.

- Subjects will take investigational drug hydroxychloroquine 200mg tablets, 4 tabs orally, once. Six to eight hours after the first dose, 3 tablets (each 200mg) will be taken. After the first day, subjects will take 1 tab (200mg) three times daily for 4 consecutive days (4

days in a row).

- On day 6 subjects will receive a phone call from the Clinical Research Coordinator and be presented with health survey.

- On day 7 subjects will have a scheduled follow-up at a USA Health Facility for repeat of nasopharyngeal swab.

- At 30 days +/- 3 days subject will receive phone call from Clinical Research Coordinator and be presented with a health survey (See Appendix A).

- There will be a 6-week +/- 2 weeks blood-draw to test for Covid-19 antibodies. Subjects will arrive to Mastin Clinic for blood draw via Clinical Research Coordinator. Subjects will also be presented with health screen survey identical to health screen survey on day 6 (See Appendix A).

ARM B: Control Arm

- On day 1 +/- 1 day Subjects will take placebo-hydroxychloroquine 200 mg tablets, 4 tabs orally, once. Six to eight hours after the first dose, 3 tablets will be taken. After the first day, subjects will take 1 tab (200mg) three times daily for 4 consecutive days (4 days in a row).

- On day 6 subjects will receive a phone call from the Clinical Research Coordinator and be presented with a health survey (See Appendix A). Increased scale score represents greater symptom severity.

- On day 7 subjects will have a scheduled follow-up at USA Health screening tent for repeat of nasopharyngeal swab.

- At 30 days +/- 3 days subject will receive phone call from Clinical Research Coordinator and be presented with a health survey (See Appendix A).

- There will be a 10-week +/- 2 weeks blood draw to test for Covid-19 antibodies. Subjects will arrive to Mastin Clinic for blood draw to be done by the Clinical Research Coordinator. Subjects will also be presented with health screen survey identical to health screen survey on day 6 (See Appendix A).

Recruitment and Compensation/Reimbursement

All subjects that meet enrollment criteria are eligible to enroll in the study as long as patient meets inclusion/exclusion criteria. Confirmation of diagnosis will be based on laboratory testing, PCR nasopharyngeal swab. In regards to all subjects, a confirmatory positive PCR nasopharyngeal swab results are not needed to start treatment. Our lab testing process of NP

swabs is taking 24 to 96 hours to return a positive result. In the case of a patient with high clinical suspicion based on exposure or symptoms per USA approved screening questionnaire (See Appendix B), the patient will also be enrolled prior to confirmatory testing. Please see inclusion section for other requirements of enrollment.

Subject will receive compensation for time and travel:

- There will be one $25.00 gift card for return to USA Health Facility and completion of second nasopharyngeal swab on day 7.
- There will be one $25.00 gift card for return to Mastin Clinic at 6 weeks visit post lab draw to compensate for their time and effort driving to USA.
- If subject completes all aspects of the trial, the subject is eligible for the (2) gift cards stated above, respectively, in the total amount of $50.00.

Drug Information:

Hydroxychloroquine

Other names: PLAQUENIL ®
Classification: Aminoquinoline; antimalarial agent
Molecular Weight: 433.95
CAS Number: 118-42-3

Mode of Action: Hydroxychloroquine has been shown to be effective against Covid-19 infection in vitro. Increases the pH of acidic intracellular organelles such as endosomes/lysosomes essential for membrane fusion, which inhibits Covid-19 entry into the cell. {Gao, 2020} {Liu, 2020}; impairs complement-dependent antigen-antibody reactions

Description: Hydroxychloroquine is a 4-aminoquinoline typically used in the treatment of malaria, rheumatoid arthritis, and lupus erythematosus.

How Supplied: Hydroxychloroquine should be ordered per standard of care methods. The investigators will supply hydroxychloroquine for this study.

Preparation: Crystalline solid, tablet, as sulphate; each tablet contains 200 mg hydroxychloroquine sulfate; equivalent to 155 mg base

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light

Stability: Stable for 2 years at specifications above

Route of Administration: Oral

Method of Administration: Subjects will take Hydroxychloroquine 200mg tablets- 4 tabs orally once, then 3 tabs orally 6 -8hours after first dose, then 1 tab three times per day for 4 consecutive days. Take with food or milk.

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential adverse effects

Sodium Chloride (placebo)

Other names: n/a
Classification: Electrolyte supplement, oral; sodium salt
Molecular Weight: n/a
CAS Number: n/a

Mode of Action: n/a; placebo

Description: Placebo drug

How Supplied: Placebo should be ordered per standard of care methods. The investigators will supply the placebo for this study.

Preparation: Tablet, oral: sodium chloride: 1.0 gram
Storage: Store at room temperature

Stability: n/a

Route of Administration: Oral tablet

Method of Administration: Subjects randomized to control arm will take 4 placebo tablets once, followed in 6 to 8 hours by 3 tablets, then 1 tablet three times per day for 4 consecutive days.

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential adverse effects.

Risks:

This clinical trial has greater than minimal risk.
Potential Adverse Drug Reactions (ADRs)

GI upset (take with food), dizziness, headache, anxiety, lack of appetite, weight loss, diarrhea, skin discoloration, hair loss, nausea/vomiting, abdominal pain, retinopathy (concentration dependent; more common with prolonged durations [> 1-5yrs] of therapy), rash/pruritus, myopathy, cardiomyopathy, bone marrow suppression (agranulocytosis, anemia, aplastic anemia, leukopenia, thrombocytopenia), hypoglycemia, suicidal ideation.

Benefits

HCQ may reduce the viral load at day 7 which will reduce the subject's symptoms and severity of disease. Reduction of the viral load also reduces the chance that subjects will spread the disease to friends, family or the general population. Early treatment thus would interrupt the transmission of disease in the community and end the epidemic.

Data Safety Monitoring Plan

Type of Research Data or Events to be Monitored:

We will capture study accruals, protocol deviations, protocol violations, unanticipated problems, and adverse events. On day 6 after initiation of the study we will call the patient to confirm next day drive thru Nasopharyngeal (NP) swab testing for viral load and, we will also complete the phone questionnaire documenting self-reported clinical status. We will ascertain for adverse events on day 6 and report serious adverse events including hospitalization with exacerbation of disease. On day 30, we will complete a phone questionnaire documenting self-reported clinical status. We will call the subject at 8 weeks post initiation of study to confirm clinic appointment and to document adverse events. At the 6-week time, we will draw blood for the antibody testing, ascertain occurrence of adverse events and answer a question about your health. We do not anticipate any adverse events occurring after the 10-week time.

Methods and Frequency of Analysis:

We will formally assess patient safety on day 6, day 30 and week 10. The department of surgery has published phone numbers for patient access and care. They can reach the on call physician and reach the PI or his designee 24/7/365 by phone. The on call physician will call the PI to report serious adverse events.

We will perform an interim analysis after 30 patients are enrolled to evaluate the efficacy, data acquisition and adherence to protocol. A summary of this information will be provided to the physicians (ID experts JV, EC, and Clinician PR) who will monitor the safety of the subjects, as well as, the DSMB.

Person(s) Responsible for Data Monitoring:

The research nurse working closely with the physicians (ID experts JV, EC, and Clinician PR) shall be responsible for reporting adverse events, protocol violations to the PI who would investigate and report serious adverse events to the IRB and FDA. We will use standard reporting to the FDA for adverse events.

Specify the name and role of the person responsible for submitting reports of unanticipated problems, adverse events, protocol deviations and protocol violations to the IRB and indicated entities (e.g. NIH, FDA, sponsor). When the investigator is the sponsor of the IND/IDE, include the plan for reporting adverse events to the FDA and, when applicable, to investigators at other sites.

Reporting Unanticipated Problems, Adverse Events, Protocol Deviations and Protocol Violations:

Unanticipated problems, adverse events, protocol deviations and protocol violations will be reported on an ongoing basis per protocol. A summary of events will be formally reported after interim analysis and within 30 days after the end of the study.

Procedures and Time Frames for Communicating Outcomes:

An interim analysis after 30 patients are enrolled to evaluate the efficacy data and adherence to protocol will be performed. Review and completion of the report will take no more than 2 weeks. The interim analysis is anticipated to occur at the halfway time point of the study. Final analysis will be obtained within 1 month of the last subject visit for blood draw.

Emergency Actions:

Unless there is an emergency, all parties are blinded with the exception of the pharmacist

Unblinding

The PI will be unblinded to the arm of the study if there is a serious adverse event deemed possibly related to study medications ie sudden death, or life-threatening allergic reaction. The unblinded pharmacist will be contacted to provide the PI with the randomization envelope for the subject.

Stopping Rules

In the event a subject is enrolled in trial based on exposure and/ or symptoms and the PCR nasopharyngeal swab results negative, the patient will be contacted to determine if there are any adverse events related to the study medication.

The study will be evaluated for safety and efficacy when 30 subjects have been randomized. Study will stop accruing if there is evidence of Serious Adverse Events (death, or serious life-threatening complications) thought to be caused by Hydroxychloroquine; for example, cardiac event with prolonged QTc interval. Enrollment will not be interrupted if the subject is taking placebo when SAE occurs. The study will also be stopped after interim analysis shows a statistically significant ($P<0.01$) reduction in % negative PCR tests at 6 days post inclusion. The safety monitors (i.e. the physicians (ID experts JV, EC, and Clinician PR) will be unblinded and they will determine if there is need to stop the study completely if SAE is related to the study.

Precautions for Maintaining Data Integrity:

On a weekly basis the PI will review with study staff adherence to the IRB-approved protocol and review validity and integrity of the data collected.

Study Monitoring, Auditing and Inspection:

The Office of Research Compliance will perform will conduct a monitoring visit after enrollment of the fifth subject. Continuing monitoring visits will occur every four weeks during active recruitment. A monitoring report will be provided to the PI, Director of Clinical Trials and the USA IRB.

Adverse Events/Serious Adverse Events

Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonization [ICH], E2A, E6). Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational product, is also an adverse event.

Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event occurring at any dose or during any use of investigational product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause under study that occurs to any subject from first day of study drug administration through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the investigational product, must be reported within 24 hours to the Coordinating Center at the University of South Alabama and Principal Investigator. Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to either product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Coordinating Center at the University of South Alabama and Principal Investigator.

SAE reports and any other relevant safety information are to be forwarded to the Coordinating Center at the University of South Alabama at kledbetter@health.southalabama.edu. All subjects

with serious adverse events must be followed up for outcome.

A copy of all 15 Day Reports and Annual Progress Reports will be submitted as required to the FDA.

Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. All AE/SAE will be reported, regardless of the grade.

Data Management and Collection

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap also provides a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the system owner. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules at the time of entry. The system was developed at Vanderbilt University but is now part of an international and multi-institutional consortium which includes the UAB Center for Clinical and Translational Science, of which the investigators of this proposal are members. REDCap has been disseminated for use locally at other institutions and currently supports 2521 academic/non-profit consortium partners in 116 countries on six continents and over 600,000 research end-users (www.project-redcap.org).

REDCap system is hosted University of South Alabama secure data center. Only IRB approved research team members will have access to the REDCap data platform. Each team member will be granted access to the REDCap data system through a secure and unique login. The database and the associated components are also part of a redundant backup strategy. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected. The award winning and widely followed implementation is in accordance to NIST 800-53 guidelines and has been vetted by all key approving parties at University of South Alabama. REDCap is also the only instance to have received an authorization to operate (ATO) from NIH/NHLBI.

Data collection for this study will be done through REDCap. All forms must be completed and submitted in a timely fashion electronically. Forms will be reviewed by the study committee for

completeness and by the DSMB for adverse event reporting.

Record Retention

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until seven years after the completion and final study report of this investigational study.

Study Budget:

This trial will be funded by the University of South Alabama, College of Medicine Department of Surgery research account.

Publication Plan:

Publication will be considered once the data analysis is complete.

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[1-29]

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APPENDIX A

SELF REPORTED SEVERITY OF SYMPTOMS SURVEY

Increased scale score indicates greater symptom severity. To be reported at Day 0, Day 6, 30 days, and 6 weeks

Score of 1	No COVID-19 illness
Score of 2	COIVD-19 symptoms present according USA Health screening tool
Score of 3	COVID-19 symptoms present according to USA Health screening tool with hospitalization
Score of 4	COVID-19 symptoms present according to USA Health screening tool with hospitalization and ICU care
Score of 5	COVID-19 with death

USA HEALTH

Coronavirus-19

As part of USA Health, it is important to remember; YOU help screen ALL patients BEFORE and WHEN they enter our health system! You ARE the solution!

During the scheduling (intake call) PRIOR to scheduling, every patient is to be asked the following:

1. ***Have you lived in or traveled outside of the United States, including China, Italy, South Korea, Iran or any other country with widespread Corona virus transmission or had contact with an individual with confirmed Coronavirus within the previous 14 days?***
2. ***Have you had a mild to severe respiratory illness with fever, cough, and have had difficulty breathing within the last 14 days?***
   https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html - use this link for additional information or continued CDC updates.

All scheduling staff and registration staff members will ask these questions **to EVERY PATIENT**.
Below are a few important reminders:

- During the **scheduling process**, if BOTH of the questions are answered with a YES – an appointment is **NOT to be made** by the scheduling staff. Additionally, if only the travel question was answered with a YES, an appointment is **NOT** to be made either. Obtain the patient information, end call with proper closing by informing patient leadership will be calling them back. Notify leadership immediately for appropriate next steps. 1st step of notification is DO, then Shelby (317-833-2723) and then Site Coordinator. Open collaborative dialogue will be disseminated to inform USA Health staff of important information or details as needed.
- *Once clarification on a few final matters are confirmed, we will communicate those immediately. Updates and changes in the process could occur on a frequent basis, so please be flexible and attentive to communications around CORONAVIRUS19 subject matters.
- Scheduling staff will document in comments tab that these questions have been asked and verified. Please include the following text:
  - *"I (staff name) verify that I have asked the screening questions on (date). They were both answered in the negative at that time."*
  - *IF they did confirm symptoms but not travel question, state, "I (name) verify that I have asked the screening questions on (date). The patient confirmed no to travel but yes to symptoms.*

USA HEALTH

Coronavirus-19

During registration at time of patient arrival, the SAME questions will be asked – *see check in resource*.

- If there is a confirmed answer with a YES, then we will **notify leadership immediately**, who will follow standard procedures for isolation purposes.
- Once patient is taken into isolation, front desk staff will follow standard universal precautions procedures and notify housekeeping to clean (based on protocol).

IF YOU HAVE QUESTIONS, AT ANY TIME, DO NOT HESITATE TO ASK! EVERY QUESTION IS IMPORTANT AS WE WORK TO KEEP OUR PATIENTS AND STAFF AS SAFE AS POSSIBLE. HANDWASHING, KNOWLEDGE, AND ACTION IS THE BEST WAY TO PREVENT SPREADING!

3.9.2020