# Treatment of Long CoronaVirus Disease (COVID) (TLC) Feasibility Trial

NCT05946551

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**PROTOCOL TITLE**: Treatment of Long COVID (TLC) Feasibility Trial: Feasibility Assessment of a Decentralized Platform Adaptive Double-Blind, Randomized Controlled Trial Investigating Repurposed Drugs in the Treatment of Post-Acute Sequelae of Coronavirus-19 (PASC)

**EXTERNAL (NON-EMORY) COLLABORATORS**

Critical Path Institute (C-Path)—Will complete an IAA

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**VERSION**: 2.0

**FUNDING SOURCE**: This study is funded by the Office of the Assistant Secretary for Planning and Evaluation (ASPE) (Prime Grant Number: 2U18FD005320) and Emory University.

**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes |
|---|---|---|
| 1 | 2.0<br><br>20_NOV_2023 | • Removal of Low Dose Naltrexone (LDN) arm from protocol<br>• Change of randomization to blinded 2:1 IP : placebos<br>• Increase stipend from $25.00 to $50.00 for screening; revise total possible compensation to $200.00<br>• Revision of IP shipping schedule to initial supply of 28 days' shipped overnight on Day 0 followed by remaining 56 days' supply with standard shipping mailed after Day 14 dose tolerance assessment.<br>• Revision of Study Schema to reflect deletion of LDN arm<br>• Moved timing of question regarding subject's most burdensome PASC symptom from Section 12 Population to Section 6.5.2 Randomization/Day 0<br>• Updated Schedule of Events to reflect protocol changes<br>• Minor grammatical and formatting corrections |
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## 1. Study Summary

| | |
|---|---|
| **Project Title** | Treatment of Long COVID (TLC) Feasibility Trial: Feasibility Assessment of a Decentralized Platform Double-Blind, Randomized Controlled Trial Investigating Repurposed Drugs in the Treatment of Post-Acute Sequelae of Coronavirus-19 (PASC) |
| **Project Design** | Fully decentralized single center, double-blind, randomized, placebo-controlled pilot feasibility trial |
| **Primary Objective** | Assess the feasibility and acceptability of methods and procedures, as determined by subjects, to be employed in a larger scale decentralized platform adaptive randomization clinical trial. |
| **Secondary Objective(s)** | • Completion rate of quality of life assessments<br>• Adherence to Investigational Product<br>• Attrition rates<br>• Safety |
| **Exploratory Objectives** | • Efficacy |
| **Research Intervention(s)/Interactions** | • Cetirizine<br>• Famotidine |
| **Study Population** | Adults ≥18 years of age with new or worsened symptoms since onset of COVID-19 that are persistent at the time of enrollment and have lasted for ≥ 12 weeks (including at least one of the following: fatigue, post-exertional malaise (PEM), headache, brain fog, sleep disturbance, dysautonomia). All subjects will be Georgia residents. |
| **Sample Size** | Up to 36 |
| **Study Duration for individual participants** | 16 weeks (4 weeks Screening, 12 weeks Treatment) |
| **Study Specific Abbreviations/ Definitions** | |

| | |
|---|---|
| AE | Adverse event |
| COVID-19 | Disease caused by SARS-COV-2 |
| CRC | Clinical Research Coordinator |
| EMR | Electronic Medical Record |
| GAD-7 | Generalized Anxiety Disorder 7-question Survey |
| HRA | Histamine Receptor Antagonist |
| IP | Investigational product |
| ITT | Intent-to-treat |
| ME/CFS | Myalgic Encephalomyelitis/Chronic Fatigue Syndrome |
| MFIS | Modified Fatigue Impact Scale |
| PASC | Post-acute Sequelae of SARS-CoV-2 |

| | |
|---|---|
| | PHQ-8 Patient Health Questionnaire 8-question survey<br>POTS Postural Orthostatic Tachycardia Syndrome<br>PP Per protocol<br>PROMIS Patient Reported Outcome Measurement Information System<br>RC Research coordinator<br>WHODAS Mean WHO Disability Assessment Schedule |
| **Funding Source (if any)** | Office of the Assistant Secretary for Planning and Evaluation (ASPE) and Emory University. |

## 2. Objectives

**Primary Objective:** The primary objective is to assess the feasibility and acceptability of methods and procedures, as determined by subjects, to be employed in a larger scale decentralized platform adaptive randomized clinical trial.

**Secondary Objectives:** Secondary objectives are to assess completion rate of quality of life assessments, adherence to Investigational Product, attrition rates and safety.

**Exploratory Objective:** The exploratory objective is to assess efficacy of histamine receptor antagonist (HRA) therapy in improving outcomes in patients with Post-Acute Sequelae of Coronavirus-19 (PASC) and at least one of the following symptoms: fatigue, post-exertional malaise (PEM), headache, brain fog, sleep disturbance, dysautonomia.

## 3. Background

In December 2019, a new human coronavirus with respiratory tropism, SARS-CoV-2, emerged in China and rapidly spread to other parts of the world [6, 7]. The coronavirus disease 2019 (COVID-19) has resulted in over 100 million confirmed cases of infection [8]. Although there are numerous publications describing the wide range of acute phase manifestations, there remains limited data on long-term sequelae of COVID-19, aka Post-Acute Sequelae of SARS-CoV-2 (PASC) or “Long COVID”. PASC may occur in 20-30% of COVID-19 patients, and symptoms result in significant impairments in quality of life [9-18]. With the growing prevalence of COVID-19, PASC is creating a substantial global burden [19]. Though common complaints include dyspnea, fatigue, brain fog, weakness, pain syndromes, anxiety, and depression, PASC can manifest as a myriad of symptoms [10, 11, 13]. In many, these symptoms can persist for >6 months, and the true duration of this disease remains unclear [13].

Though the underlying pathophysiology of PASC symptoms remains unknown, several mechanisms have been proposed in individuals with no detectable parenchymal or structural damage resulting from acute COVID-19 infection. SARS-CoV-2 can persist in bodily

fluids for a prolonged period extending beyond the acute viral phase, but little is known about the clinical relevance of this finding [20,21]. Concern exists that persistent viral reservoirs remain undetected, promoting ongoing, heightened immune responses contributing to the myriad of symptoms seen in PASC [22]. Furthermore, natural killer (NK) cells appear to play an important role in the innate immune response to COVID-19, wherein diminished NK cell response is associated with viral persistence and increased mortality [23]. Reduction in NK cell number and function occurring in COVID-19, particularly severe infections, results in decreased clearance of infected cells and unchecked elevation of tissue-damaging inflammation markers. SARS-CoV-2 infection skews the immune response towards an overwhelmingly inflammatory phenotype. Restoration of NK cell effector function has the potential to correct the delicate immune balance required to effectively overcome SARS-CoV-2 infection [24]. Others suggest that PASC is mediated through non-viral inflammatory mechanisms, such as mast cell activation syndrome (MCAS), which may explain the inflammatory, multisystem nature of PASC symptoms [25]. Here it is posited that a dysfunctional population of mast cells become hyper-stimulated in a continuous activation loop, leading to the heterogeneous clinical presentations seen in PASC patients. Also proposed is an autoimmune link, wherein hosts lose tolerance to auto antigens due to molecular mimicry between pathogen and host proteins leading to dysregulated immune response. Autoantibodies opposing B cells, various cytokines, and cellular membrane components have been identified in patients with severe acute COVID-19, though studies demonstrating this processing in PASC remain sparse [26-28].

A host of medications have been investigated in the treatment of acute COVID-19, though few drugs have been studied in formal randomized controlled trials in the post-acute phase to address persistent symptoms and long-term sequelae. A panel assembled by the CURE Drug Repurposing Collaboratory (CDRC) – a public-private partnership - that includes at least one of each of the following—physician, pharmaceutical engineer, pharmacist, public health professional, immunologist, patient, and drug repurposing expert—reviewed the available data for over 60 candidate therapeutic approaches. Several drugs appeared to be promising based on early anecdotal reports and plausible mechanisms. Given the urgency of finding answers and the need for randomized controlled trials to begin to determine drugs that are effective for PASC, the panel selected the following treatment as an initial approach.

As mast cell activation syndrome is one theorized mechanism of severe acute COVID-19 and a proposed physiologic derangement contributing to PASC, histamine receptor antagonists (HRA), such as famotidine and cetirizine, have garnered interest as possible drug candidates. (See section 5.1.2). These agents may modulate their effects through reductions in cellular inflammatory mediators, such as histamine, serotonin, TGFb, VEGF, IL6, IL8,

interferons, and NETs and modulation of dysregulated T cells. Administration of HRAs in a relatively small cohort of PASC patients (N=25) demonstrated a 72% improvement in patient reported symptoms, of which, 20% had complete symptom resolution [34]. This is compared with those who received no treatment (N=40) who experienced a 50% improvement, with complete resolution in 4% in the same period.

## 4. Study Endpoints

**Primary endpoint:**

- Subject reported (patient reported outcome [PRO]) end of study questionnare

**Secondary endpoints:**

- % subjects who complete 70% of PRO surveys/questionnaires at 12 weeks
- % subjects who complete 70% of IP doses through 12 weeks
- % subjects Lost to Follow Up (LTFU)
- % subjects voluntarily terminate participation
- Incidence of adverse events and serious adverse events
- Number of discontinuations or temporary suspensions of IP

## 5. Study Intervention/Investigational Agent

### 5.1 Cetirizine

Cetirizine is a histamine receptor antagonist (HRA). It will be dispensed as a 10mg capsule with instructions for subjects to take one capsule daily by mouth. Subjects will be instructed to take the IP as close to the same time every day as possible, preferably at bedtime.

### 5.2 Famotidine

Famotidine is a histamine receptor antagonist (HRA). It will be dispensed in 20mg capsules with instructions for subjects to take one capsule twice daily, as close to the same time every day as possible.

### 5.4 Pharmacokinetics

#### 5.4.1 Cetirizine

Cetirizine hydrochloride is a second-generation antihistamine that selectively antagonizes peripheral histamine (H1) receptors [34]. Glomerular filtration is the predominant mode of renal elimination for the predominately unmetabolized drug, which has minimal liver metabolism or CYP450 interaction. The half-life is

8.3 hours with preserved renal function and 24.9 hours with moderate to severe renal impairment.

#### 5.4.2 Famotidine

Famotidine hydrochloride selectively antagonizes peripheral histamine (H2) receptors [33]. Glomerular filtration is the predominant mode of renal elimination for the predominately unmetabolized drug, which has minimal liver metabolism or CYP450 interaction. The half-life is 2.5 hours with preserved renal function and 20 hours with severe renal impairment.

### 5.5 Placebo

The investigational pharmacy will provide placebo capsules manufactured to match each study treatment for oral administration.

The HRA placebos will be designed as capsules of the inert substance microcrystalline cellulose and will match the morphology of the respective HRA treatment capsules.

### 5.6 Storage and Stability

All IP will be stored at USP controlled room temperature 20°-25° (68°-77 °F). Excursions between 15° and 30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°, transient spikes up to 40° are permitted as long as they do not exceed 24 h. Participants will be instructed to maintain their IP under these conditions. IPs will be maintained in a tight, child-proof container.

Control of the IPs used in this protocol will be accomplished by following the established, approved organizational SOPs of the Emory Investigational Drug Service (IDS) regarding protocol management and IP accountability, IP storage, temperature monitoring, randomization by unblinded pharmacists, dose preparation, IP labeling, and shipping of study medication to subjects.

### 5.7 IND

Dr. [redacted] holds the IND #162060 and is acting as the Sponsor-Investigator for this study.

### 5.8 Provision of Investigational Product to Participants

Following receipt of confirmed subject eligibility and consent, IDS will randomize subjects as described below in Section 6.1. IDS will prepare the courier or overnight mail service, which will deliver IP to participants according to the below dosing schedule.

Clear instructions will be provided to the subject regarding the number and type of capsules to be ingested at each IP administration time point listed.

**DOSING SCHEDULE**

**Antihistamine and Placebo Arm Dosing** [1,2]

**Day 0-Day 84:**
Cetirizine 10 mg or placebo (1 capsule) QD
Famotidine 20mg or placebo (1 capsule) BID

1. Dose to be assessed at Day 14. Subjects unable to tolerate will be withdrawn from study
2. Subjects receive initial shipment of 28 days' supply at Day 0, and shipment of remaining 56 days' supply after Day 14 assessment

### 5.9 Acquisition

A sufficient quantity of the FDA-approved or compounded formulation of famotidine, cetirizine and placebo for the study will be purchased and distributed by the Emory Investigational Drug Services (IDS). Emory IDS was chosen because of its experience in the compounding of medications for clinical trials, available formulations and strengths, assays for potency, and ability to provide matched placebos.

### 5.10 Accountability and Destruction Procedures

Subjects will not be required to return any excess drug capsules to the facility. Subjects will dispose of excess drug capsules locally, ensuring that the child-protection closure system is intact.

### 5.11 Treatment Adherence

Treatment adherence will be measured by subjects completing a weekly assessment of their IP adherence by completing a study adherence log. The CRC will also review remaining pill count with the subject during study visits to inform adherence.

## 6. Procedures Involved

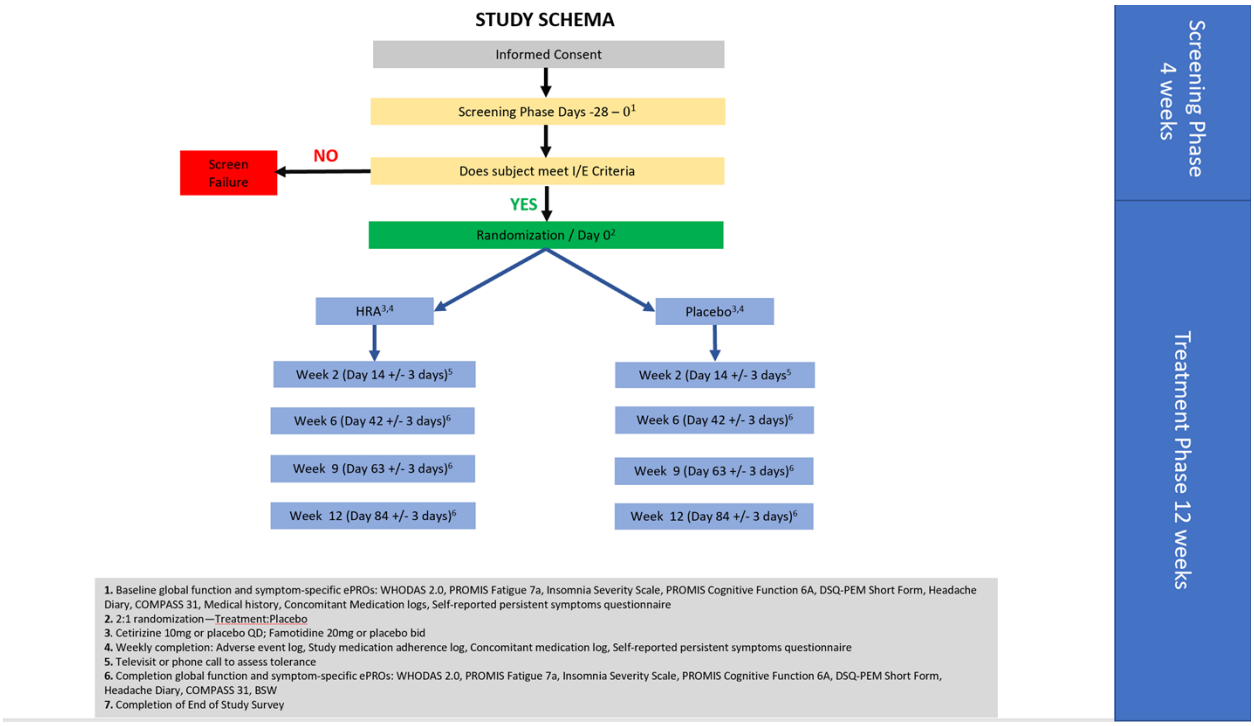
### 6.1 Study Design

This is a fully decentralized, single center, randomized, double-blind, placebo controlled, clinical trial to evaluate the safety, tolerability, and feasibility of a potential treatment for PASC.

Upon confirmation of eligibility, the investigational pharmacist will randomize subjects 2:1 treatment versus placebo. Treatment consists of 10mg of cetirizine daily and 20mg of famotidine twice daily. Placebos will match the morphology of the treatments but contain no active ingredients. Study subject and study team will be blind to assigned treatment; only the IDS will be unblind.

Subjects will be followed for safety, tolerability, and responses to patient reported outcome (PROs) over 12 weeks. At Week 12, End of Study, subjects will be required to complete a questionnaire that addresses several aspects of feasibility of participating in the study.

## 6.2 Study Schema




## 6.3 PRO Collection—Feasibility and Efficacy Assessments

Subjects will complete the following PROs at protocol specified timepoints as described in Section 6.5 and as detailed in the Schedule of Events in Section 6.7. Subjects with difficulty completing the PROs in Emory's Part 11 compliant REDCap instance will be contacted by CRC via telemedicine or telephone. In these encounters, CRC will administer PRO surveys and collect symptom tracking data at protocol designated study time points.

- **PROMIS Fatigue 7A**—measures fatigue with daily activities
- **Insomnia Severity Scale**—measures difficulty sleeping
- **PROMIS Cognitive 6A**—measures difficulty thinking and concentrating
- **DePaul Symptom Questionnaire (DSQ-1) Short form**—measures post-exertional malaise
- **COMPASS 31**—measures symptoms of dysautonomia

- **WHO Disability Assessment Schedule (WHODAS 2.0)**—measures health and disability
- **Headache Diary**—measures the number and severity of headaches (completed daily during the 7 days prior to study visit)
- **Self-reported Persistent Symptoms Survey**—measures presence or absence of Long COVID symptoms and their severity
- **Concomitant Medications Log—**records subject-reported medications, supplements and vitamins
- **Self-reported Changes to Health Log—**records subject-reported adverse events
- **IP Adherence Log**—records subject-reported adherence to IP dosing regimen
- **End of Study Survey**—assesses the feasibility and acceptability of methods and procedures

### 6.4 Safety Assessments

Subjects will report signs and symptoms of changes to their health weekly. In addition to examining the subject's electronic medical record (EMR), the CRC will assess for AEs and SAEs by reviewing the subject's AE log and talking to the patient. AEs and SAEs will be reported as defined by 21 CFR 312. All SAEs must be followed until resolution/stabilization or until a time that is determined by the Investigator.

### 6.5 Detailed Study Procedures and Assessments by Study Period/Study Day

The procedures performed during this study will be performed according to this section and the Schedule of Events table shown in Section 6.7 below.

#### 6.5.1 Screening (Within 28 days ± 3 days of Day 0):

Prior to any study-specific procedures or data collection, the CRC will obtain informed consent from potentially eligible subjects. If the subject is not an Emory patient, the subject will be asked to sign a medical release form. Using a verbal consent, subjects will be prescreened by televisit by the CRC who will review the inclusion/exclusion criteria. Subjects who remain interested and are potentially eligible will then be consented, and medical records will be sought from the subject's healthcare system to confirm eligibility.

The following procedures and data collection will be performed during Screening:

- Signature of electronic Informed Consent Form and provision of subject information

- Collection of sociodemographic data
- Medical record review
- Collection of medical and surgical history, including acute COVID-19 history, PASC history (time from symptom onset or positive SARS-CoV-2 testing), and COVID-19 vaccination status
- Assessment routine concomitant medications
- Assessment of baseline PROs:
    - WHODAS 2.0 36-item score
    - PROMIS Fatigue 7a
    - Insomnia Severity Index
    - PROMIS Cognitive Function Short Form 6A
    - DSQ-PEM Short Form
    - Headache Diary (completed daily during the 7 days prior to visit)
    - COMPASS 31
- Confirm Inclusion and Exclusion criteria

**6.5.2 Randomization/Day 0** will be a televisit with the study physician for a baseline evaluation to confirm eligibility. Study clinician will confirm adequate hepatic and renal function after onset of Long COVID symptoms through review of participant's labwork in historical medical records. Study clinician will confirm negative pregnancy status in participants capable of becoming pregnant via urine or serum β-HCG within 30 days of randomization/Day 0. Women of childbearing potential who don't anticipate a pregnancy test at a clinician's office within 30 days of randomization will be mailed a urine pregnancy test kit by study staff. Subjects will take the pregnancy test during the Randomization/Day 0 televisit and show the result to the study physician. If additional physical exam is needed per study physician discretion, the study physician will conduct a telemedicine exam of the following systems: Constitution, Head, eyes, ears, nose and throat, Cardiovascular, Respiratory, Gastrointestinal, Genitourinary (CVA tenderness per subject exam), Musculoskeletal, Skin, Neurological, Psychological. Subjects will be asked to report their most burdensome PASC symptom at Day 0.

Upon confirmation of eligibility, subjects will be randomized as described in Section 6.1 and shown in Section 6.2.

**6.5.3 Day 1:** Participant receives IP and self-administers.

**6.5.4 Days 2-84**: Participant takes IP daily

**6.5.5 Weekly:** Participant completes adverse event log, study medication adherence log, concomitant medication log, self-reported persistent symptoms questionnaire

**6.5.6 Days 42, 63, and 84, all +/- 3 days,** subjects enter patient reported outcome (PRO) data into REDCap.

- PRO data to be collected
  - WHODAS 2.0 36-item score
  - PROMIS Fatigue 7a
  - Insomnia Severity Index
  - PROMIS Cognitive Function Short Form 6A
  - DSQ-PEM Short Form
  - Headache Diary (completed daily during the 7 days prior to visit)
  - COMPASS 31

**6.5.7 Day 84/End of Study (EOS) or Early Termination:** Participants complete End of Study survey

### 6.6 Subject Contact Schedule

Subject contact will occur at designated time points per protocol via televisit or phone call. To ensure data quality, study personnel may contact subjects at unscheduled timepoints to obtain clarifying information on adverse events, provide supplemental training on REDCap data entry, or to remind overdue participants to complete the scheduled patient-reported outcome surveys according to the study schedule. Study subjects may also initiate unscheduled contact with study staff for help with any questions, concerns, or difficulties.

### 6.7 Schedule of Events

| | Screening | | | | Rand | Dose 1 | Treatment Phase | | | | | | | | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Weeks** | **Week -4** | **Week -3** | **Week -2** | **Week -1** | **Week 0** | | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** | **Week 8** | **Week 9** | **Week 10** | **Week 11** | **Week 12** |
| **Days** | **Day -28** | **Day -21** | **Day -14** | **Day -7** | **Day 0** | **Day 1** | **Day 7** | **Day 14** | **Day 21** | **Day 28** | **Day 35** | **Day 42** | **Day 49** | **Day 56** | **Day 63** | **Day 70** | **Day 77** | **Day 84** |
| **Visit Window**[a] | | | | | ± 3 days | +3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | X | | | | | | | | | | | | | |
| Subject app training | X | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Concomitant Medications | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Telehealth Physical Exam[b] | X | | | | X | | | | | | | | | | | | | |
| Medical/Surgical History[c] | X | | | | X | X | | | | | | | | | | | | |
| Dispense (mail) UPT[d] | X | | | | | | | | | | | | | | | | | |
| UPT[d,e] | | | | | X | | | | | | | | | | | | | |
| Query for subject-assessed worst symptom | | | | | X | | | | | | | X | | | X | | | X |
| Randomization | | | | | X | | | | | | | | | | | | | |
| Dispense IP | | | | | X | | | X | | | | | | | | | | |
| IP Dosing | | | | | | Day 1 daily through End of Study (Day 84) | | | | | | | | | | | | |
| Tolerability assessment | | | | | | | | X | | | | | | | | | | |
| IP Adherence Log | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X |
| WHODAS | | | | X | | | | | | | | X | | | X | | | X |
| DSQ-PEM | | | | X | | | | | | | | X | | | X | | | X |
| PROMIS Fatigue 7a | | | | X | | | | | | | | X | | | X | | | X |
| Insomnia Severity Scale | | | | X | | | | | | | | X | | | X | | | X |
| Headache Diary[g] | | | | X | | | | | | | | X | | | X | | | X |
| PROMIS Cognitive Function 6a | | | | X | | | | | | | | X | | | X | | | X |
| COMPASS 31 | | | | X | | | | | | | | X | | | X | | | X |
| Symptom Survey | | | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Event Collection[c] | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Televisit or telephone contact[h] | X | | | | X | X | | X | | | | X | | | X | | | X |
| Issue Stipend | | | | | X | | | | | | | X | | | X | | | X |
| End of Study Survey | | | | | | | | | | | | | | | | | | X |

a. Visit weeks and windows are calculated from Day 1
b. Telehealth PE to be completed at any time during Screening Phase or on Day 0 pre-randomization, if not available in medical records
c. Med/Surg Hx collected up to time of first dose; AE collected after completion of first dose
d. For WOCBP
e. UPT conducted during Day 0 televisit with visual confirmation of results
f. Subjects receive initial shipment of 28 days' supply at Day 0, and shipment of remaining 56 days' supply after Day 14 assessment
g. Headache diary to be completed in REDCap daily Days -7 to Day -1 and daily for the 7 days preceding SVs at Weeks 6, 9 and EOS
h. Televisit/telephone call required at Days -28, 0, 1, 14 and as needed for dose tolerability assessment and query resolution at subsequent SV days. Unscheduled visits at request of study team or subject are permitted.

## 7. Statistical Analysis Plan

### 7.1 General Considerations and Overall Design

Prior to performing any analyses, the data will be 1) screened for entry errors; 2) checked for outliers; 3) assessed for patterns of missing data.

### 7.2 Population for Analysis

The following populations will be used in the analyses:

- Intent-to-treat (ITT): All subjects who received at least one intake of IP. Subjects will be analyzed according to their assigned treatment.

- Per protocol (PP): All subjects in the ITT population who were free from major protocol violations that could lead to bias
- Safety: All subjects who received at least one intake of IP. Subjects will be analyzed according to the treatment they actually received.

### 7.3 Analysis for Primary Outcome

We will tabulate responses to determine frequency of difficulty understanding IP schedule, difficulty adhering to dosing schedule, difficulty using the REDCap interface, satisfaction with online study procedures, satisfaction with study staff interactions and availability, satisfaction with the frequency and volume of data collection, and difficulty with completing surveys. We will review comments from participants to identify barriers and facilitators to optimize the full-scale TLC trial.

### 7.4 Analysis for Secondary Outcomes

#### 7.4.1 Attrition

Attrition will be tabulated as the proportion of subjects who complete at minimum 70% of surveys at 12 weeks, the proportion of subjects who complete at minimum 70% of doses through 12 weeks, the proportion of subjects Lost to Follow Up (LTFU), and the % subjects that voluntarily terminate participation.

#### 7.4.2 Safety

AEs and SAEs will be tabulated by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), by System Organ Class (SOC) and by severity. The subset of AEs that are assessed by the Investigator as having a relationship to the IP will be considered to be treatment-related AEs. The number and percentage of AEs and treatment-related AEs will be tabulated by treatment arm and overall. AEs will also be summarized by severity, relatedness and seriousness. AEs will be analyzed both by ITT and by treatment received, in the Safety Population. Comparisons of rates of AEs will be presented descriptively.

### 7.5 Analysis for Exploratory Outcomes

#### 7.5.1 Efficacy

Responses to ePROs (WHODAS 2.0 36-item score, PROMIS Fatigue 7a, Insomnia Severity Index, PROMIS Cognitive Function Short Form 6A, DSQ-PEM Short Form,

Headache Diary, COMPASS 31) will be tabulated and change in response between baseline and each study visit (6, 9, 12 weeks) will be calculated. Comparisons of changes in responses will be made between subjects receiving study drug versus placebo.

### 7.5 Subject Disposition

The disposition of all subjects in the various populations will be summarized by treatment arm as follows:

- Number of subjects randomized
- Number of subjects who completed the study
- Number of subjects who discontinued IP
- Number of subjects who withdrew from the study
- Number of subjects lost to follow-up

All subjects who discontinued the study will be listed by treatment arm with the reason for discontinuation, if available

## 8. Data and/or Specimen Banking

Data will be shared among members of the study team with appropriate access based on study role, training, and delegation of authority. Data will be made available to assigned study monitors, the appropriate oversight authorities, the Food and Drug Administration, and other state and federal regulatory authorities as required by state and federal law.

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

The study will be registered with one or more recognized clinical study registries, e.g., www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to regulatory authorities or shared with research institutions, as needed.

The final Clinical Study Report will be submitted to the ethics committee and regulatory authorities, if required.

The Sponsor encourages the communication and/or publication of the results by the consortium of partners in accordance with the terms of the Clinical Trial Agreement.

Subjects will have the option of consenting to be contacted for future related studies. If subjects choose this option, their name and contact information will be stored in a password-protected file stored on a secure, Emory server.

**9. Sharing of Results with Participants**

Individual subject results will not be shared with participants. Participants interested in knowing their randomization assignment may request that staff release that information after unblinding occurs after database lock. Participants desiring study results may request that staff provide them links to any publications resulting from the trial.

Incidental findings are not anticipated in this study because there are no investigational diagnostic tests. However, if we discover a medical issue that is unrelated to the purpose of this study, we will share that information if it is of urgent medical importance.

**10. Study Timelines**

- The duration of participation for each individual subject will be 16 weeks—4 weeks Screening, 12 weeks Treatment.
- Based on the current epidemiology, the duration of recruitment should be approximately four (4) months from first subject enrolled.
- Last subject last visit is anticipated to occur in August 2024. The estimated date for the investigators to complete primary analyses is February 2025.

**11. Inclusion and Exclusion Criteria**

- CRC will pre-screen Emory and Grady PASC Clinic patients for potential eligibility via chart review and will contact the clinic physician regarding potentially eligible patients. CRC will request clinic physician advise patients of the study and provide CRC/study team contact information to interested patients. CRC/study team will describe the study to these potential subjects and will send the ICF to interested patients for the ICF discussion.
- Non-Emory subjects will contact CRC/study team in response to recruitment advertisements. CRC/study team will confirm the potential subject is 18 years of age or older and a Georgia resident with new or worsened symptoms of interest since onset of COVID-19 that have lasted for ≥ 12 weeks. CRC/study team will describe the study to

these potential subjects and will send the ICF to interested subjects to conduct the ICF discussion.

- Potential subjects will not complete baseline questionnaires and CRC/study team will not conduct a full medical/surgical history and concomitant medication review for inclusion/exclusion prior to the subject signing the ICF.

***Inclusion Criteria:*** A subject must meet all of the following criteria to be eligible for this study:

1. Adults ≥18 years of age with history of a SARS-CoV-2 PCR positive test and/or medical records from healthcare provider that coincides with the diagnosis of long-COVID
2. New or worsened symptoms since onset of COVID-19 that are persistent at the time of enrollment and have lasted for ≥ 12 weeks (including at least one of the following: fatigue, post-exertional malaise (PEM), headache, brain fog, sleep disturbance, dysautonomia).
3. Confirmation of negative urine or serum HCG (pregnancy) test in women of child-bearing potential
4. Willing to use appropriate contraceptive for female and male subjects for the duration of the study
5. Has an address (for mailing of IP) in the state of Georgia
6. Able to swallow capsules
7. Has reliable access to a mobile phone, tablet, laptop, or desktop computer capable of connecting to the internet via WiFi or a data plan
8. Available lab work (CBC and CMP) after onset of long COVID symptoms
9. Willing and able to comply with scheduled visits, treatment plan, and other study procedures including receiving either intervention or placebo
10. Willing to not take any of the study medications while enrolled in the study except for essential need as prescribed by a healthcare provider

***Exclusion Criteria:*** A subject who meets any of the following criteria will be excluded from this study:

1. No PASC symptoms at the time of enrollment or PASC symptoms present <12 weeks at the time of enrollment
2. Inability to provide own informed consent
3. Currently hospitalized

4. For Women of Child Bearing Potential (WOCBP)*: currently pregnant or plans to become pregnant during study period; for males with partners OCBP, plans to become pregnant during study period
5. Actively enrolled in another Long COVID/PASC interventional trial or participation in another interventional clinical trial in the last 30 days or planned during the trial period
6. Unstable medical comorbidities (e.g., decompensated cirrhosis, stage III-IV chronic kidney disease, NYHA class III congestive heart failure), per subject report, telemedicine physical exam, baseline laboratory values (hematology and extended chemistry panels) and/or medical records
7. Other medical conditions occurring either before or after onset of COVID-19 that can otherwise account for PASC-type symptoms (examples include, but are not limited to: uncontrolled thyroid disease, adrenal insufficiency, chronic fatigue syndrome, Postural Orthostatic Tachycardia Syndrome (POTS), among others). This will be up to the discretion of the study physician.
8. Currently immunocompromised from the following: solid organ transplant, BMT, high dose steroids (>20mg prednisone per day), immune modulators, or chemotherapy
9. Currently taking opioid analgesics, undergoing treatment for opioid addiction, or taking any other prohibited concomitant medication
10. Opioid dependence or withdrawal syndrome
11. Known sensitivity or adverse reaction to H1 or H2 receptor antagonists, or medication components
12. Suspected or confirmed pregnancy or breastfeeding
13. Already on H1 or H2 receptor antagonists within 3 months of randomization
14. Currently receiving other therapies to treat COVID-19 or Long COVID symptoms, e.g., convalescent plasma, remdesivir, Paxlovid

*WOCBP are defined as a person of childbearing ability who has not had a hysterectomy and/or both tubes and/or both ovaries removed and/or is not postmenopausal and over the age of 45).

**12. Population**

The study population will consist of Georgia residents ages ≥18 years with new or worsened symptoms since the onset of COVID-19 that are persistent at the time of enrollment and have lasted for ≥ 12 weeks. Subjects must have at least one of the following PASC symptoms: fatigue, post-exertional malaise (PEM), headache, brain fog, sleep disturbance, or dysautonomia.

The following special populations will not be enrolled in this study:

- Adults unable to consent

- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Cognitively impaired or Individuals with Impaired Decision-Making Capacity
- Individuals who are not able to clearly understand English

This study will use the 2020 US Census classifications for race and ethnicity data as established in the 1997 Office of Management and Budget (OMB) Standards and described at: https://www.govinfo.gov/content/pkg/FR-1997-10-30/pdf/97-28653.pdf. Race categories will include American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Some Other Race. More than one race may be selected. Ethnicity will ask if subjects are or are not of Hispanic, Latino/a/x or Spanish origin. Both race and ethnicity will include a write-in section in which participants can self-identify.

Racial and ethnic classifications of subjects will be used for descriptive statistics, but will not be used within an explanatory model (as a covariate).

**13. Vulnerable Populations**

This trial will not enroll subjects who are members of vulnerable populations.

**14. Local Number of Participants**

24 subjects are needed to complete the research procedures. We anticipate enrolling and screening approximately 36 subjects to reach this goal, given screen failure and possible study drop-out/withdrawal. Screen failures will be replaced; drop-out/withdrawal/lost to follow-up will not be replaced. Participants will be drawn from the state of GA. We project enrollment to reflect the incidence of PASC between the sexes of 70% female and 30% male. PASC incidence among races is unknown.

**15. Recruitment Methods**

Recruitment will be done through a two-pronged approach utilizing direct engagement with Long COVID clinics at Grady and Emory.

We will engage with clinicians at PASC and primary care clinics at Emory and Grady. Promotion will entail a combination of direct outreach and education from our team along with materials such as flyers and pamphlets.

The study team will review medical records for Emory and Grady PASC Clinic patients to identify potentially eligible prospective subjects, per protocol Section 11 Inclusion and Exclusion Criteria.

Finally, we will share our graphics with Emory's communications team and request placement on their website and dissemination of information about the trial.

## 16. Withdrawal of Participants

Participants may discontinue IP or withdraw from the study at any time and for any reason without prejudice to their medical care. Furthermore, the PI may discontinue a subject from IP or withdraw them from study procedures. The reason for the patient's discontinuation or withdrawal will be recorded in REDCap.

### 16.1 Discontinuation of IP

Discontinuation refers to the subject stopping IP administration. Subjects who discontinue IP should, with their consent, continue participating in the study, completing all visits and assessments as scheduled. The reason for IP discontinuation will be recorded in REDCap.

Possible reasons for IP discontinuation are:

- If the subject requests discontinuation of treatment with IP
- If the subject requires treatment with a prohibited concomitant medication
- If the subject develops contraindications to any of the IPs
- If clinical reasons arise where the harm is considered to outweigh the benefits by the Investigator
- If the subject no longer meets inclusion/exclusion criteria
- Occurrence of intolerable adverse reactions and pregnancy
- Unblinding (accidental or medically necessary) of subject, investigator, or study staff

### 16.2 Withdrawal from Study Procedures

Withdrawal refers to a study participant's stopping IP and all study assessments and visits.

If a subject withdraws his/her consent for future collection of information, the Investigator may retain and continue to use any data collected before consent was withdrawn.

Every effort should be made to ensure that subjects who withdraw or are withdrawn undergo an early withdrawal study visit as soon as possible.

Possible reasons for withdrawal include:

- The subject requests to withdraw

- The subject withdraws consent to the collection, use and sharing of his/her data
- The Investigator thinks that study participation is no longer in the best interest of the subject
- The Investigator thinks that the subject is at significant risk of failing to comply with the provisions of the protocol so as to cause harm to her/himself or seriously interfere with the validity of the study results
- At the request of the ethics committee or regulatory authorities in the exercise of their duties
- Loss to follow-up
- The study is terminated

All data from subjects withdrawn from the study may be analyzed up until time of withdrawal.

### 16.3 Loss to Follow-Up

A study subject will be considered lost to follow-up if s/he stops entering data into REDCap and can no longer be contacted by study personnel. Before the subject can be considered as lost to follow-up, study personnel must make every effort to re-establish contact with a minimum of 3 documented contact attempts by phone, text and/or email. These contact attempts will be documented in a note in the subject's study record in REDCap. Information on subject status, i.e., alive or dead, hospitalized, should be collected and procedures for AE/SAE followed as appropriate.

If all attempts to re-establish contact with the subject are unsuccessful, s/he will be considered to have withdrawn from the study and the primary reason of loss to follow-up will be recorded in the eCRF, if available.

### 16.4 Screen Failure

A subject who discontinues study participation for any reason after signing the informed consent form but before randomization, is regarded as a "screen failure."

## 17. Risk to Participants

The most important risks or discomforts a participant may expect from taking part in this research are the common side effects of the IPs.

### 17.1 Cetirizine

Cetirizine is a well-tolerated nonprescription drug. Common side effects (greater than 2%) include somnolence, fatigue, dry mouth, pharyngitis, dizziness, headache, and nausea. Other adverse events, including serious adverse events, as reported in the label, were observed infrequently (less than 2%) in U.S. trials with more than 3,500 adults and children 12 years and older. No causal relationship of these infrequent events with cetirizine administration has been established.

### 17.2 Famotidine

Famotidine is a well-tolerated nonprescription drug. Common side effects (greater than 1%) that have been observed in controlled clinical trials and may be causally related to famotidine therapy include headache, dizziness, constipation, and diarrhea. The marketing label reports other adverse reactions, including serious adverse reactions observed infrequently in clinical trials and post-market surveillance. The relationship of these adverse reactions to famotidine therapy is unclear.

### 17.3 Prohibited Concomitant Medications

For further details concerning warnings, precautions, and contraindications, refer to package inserts. During the study, participants cannot take the following medications outside of the IP: antihistamines (cetirizine, loratadine) anti-acid H2 blockers (famotidine, ranitidine), naltrexone, suboxone, methadone, tramadol, Paxlovid, or opioids.

## 18. Potential Benefits to Participants

There are currently no treatments known to be effective for PASC. Individual participant's Long COVID symptoms may improve or resolve.

## 19. Compensation to Participants

Subjects will receive a $50.00 stipend for their time and effort upon completion of the Screening Phase, and after completion of study assessments at Days 42, 63 and 84 (Weeks 6, 9 and 12).

Completion of the Screening Phase is defined as 1. completing all baseline assessments, with or without assistance from the study team, and 2. completing the Day 0 visit. Subjects who complete both elements, whether they screen fail or randomize, will be eligible for a stipend. As baseline assessments are essential to ensuring subject safety and eligibility, subjects who consent but don't complete all assessments, withdraw or are withdrawn prior to the Day 0 visit, or are lost to follow up during screening are ineligible to receive the $25.00 stipend.

Stipends will be issued via reloadable debit card, e.g., GreenPhire ClinCard. Tax information is not required as total possible compensation is $200.00. Subjects who withdraw early will receive payment for any visits for which stipends are paid that they complete.

## 20. Data Management and Confidentiality

### 20.1 Survey Data Collection

Participants will be asked to record their IP adherence, report initiation of new routine medications, and report adverse side effects weekly throughout the trial on electronic forms in Emory's Part 11 compliant REDCap instance.

Adherence with taking the medication will be assessed via self-report weekly in REDCap.

In all protocol-specified data, subjects will be identified only by coded numbers in order to maintain confidentiality.

### 20.2 Clinical Data Collection

Clinical data on comorbid diseases, lab values, e.g., CBC, CMP, medications, acute COVID-19 disease course and treatment, as described above, may be collected from participants' EHR using participant name and medical record number.

### 20.3 Data Handling and Integrity

Case report form data will be entered in and maintained on a 21 CFR part 11 compliant Electronic Data Capture system (EDC) with appropriate access controls via Emory's Part 11 compliant REDCap instance. Both study subjects and study staff will enter data into this system.

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

The Trial Master File (TMF) will be electronically maintained in Emory's OneDrive, with access restricted to the Sponsor, Lead CRC and assigned PM, if applicable. CRCs will grant access to the assigned CRA upon request on an as needed basis.

The Investigator Site File (ISF) will be electronically maintained in Emory's OneDrive with access restricted to the PI, SIs, and CRC. CRCs will grant access to the assigned CRA upon request on an as needed basis.

The site will maintain an electronic screening log in Emory's OneDrive containing the screening number, name, date of birth, age, sex and, if applicable, reason for screen failure. An electronic Subject ID log of all subjects randomized in the study will also be kept in Emory's OneDrive. This log will contain Subject ID Number, name, address, telephone number, email, emergency contact name and phone number. Access to both these logs will be restricted to the PI, SI and CRC.

The PI will manage oversight of quality control for collected data. Enrollment of subjects will be performed using inclusion/exclusion criteria defined above. Study data will be recorded into a REDCap database, which is HIPAA compliant, part 11 compliant, password protected with variable assignable security access, and maintains an audit trail consistent with all regulatory requirements for maintenance of clinical trial data. Data summaries and quality control checks will be run routinely.

Data collection, review and 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 PI. A study monitor will review the electronic consent documents, IP administration data, and SAE reporting. At the monitor's discretion, a random sampling of subjects may undergo full evaluation and comparison of source documentation with data entered into the study database.

### 20.4 Missing Data

Research coordinators will make a consistent effort to ascertain all study data within the protocol specified windows, as well as outside these windows as needed. Participants who fail to respond will be contacted by study staff multiple times, and emergency contacts may be contacted as well, prior to being recorded as lost to follow-up. All data collected on a participant prior to loss to follow-up or withdrawal of consent will be included in analyses.

### 20.5 Data from Screen Failures

The following minimum data will be recorded in the eCRF for screen failures:

- Subject identification number
- Demographic data, i.e., sex, year of birth and/or age
- Reason for screen failure
- Date of ICF signature
- Date of Screen Failure

### 20.6 Protection of Confidentiality

All standard confidentiality procedures will be observed for this study. Research staff will be trained on protocol and GCP standards before they will be allowed contact with participants or data. All data will be stored in a secure HIPAA compliant manner. No subject identifiable data will be stored on individual research computers or flash drives. Data transfers will contain only deidentified data; subjects will be identified only by coded numbers. Subject data will only be released with the subject's written permission, except as necessary for monitoring, auditing, or inspection by authorized entities. If the results of the study are published, the subject's identity will remain confidential.

## 21. Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

**X More than minimal risk**

Review our Data and Safety Monitoring Questionnaire and insert the relevant monitoring table at the end of this section. Also upload the completed questionnaire in the "Basic Study Information" smartform section in eIRB, question #8, as a separate document.

Mark the risk categorization, as determined by the Data and Safety Monitoring Questionnaire, that applies to your study below:

| Select one of the following (do not delete this table; review the guidance document for definitions): | |
|---|---|
| ☐ Medium Complexity | |
| ☐ High Complexity Category A | |
| ☒ High Complexity Category B<br>*If choosing this category for a study under an IND or IDE because you believe the study intervention does not significantly impact morbidity or mortality, please provide your rationale:*<br>The IPs are FDA approved and will be administered at doses which are within the recommended doses for the registered indications of the products | |

| **DSMP Requirement** | **How this Requirement is Met** | **Frequency** | **Responsible Party(ies)** |
|---|---|---|---|
| Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol. | *There should be a standard operating procedure to review data (whether a sample or 100%) at pre-determined intervals to ensure that there is adequate documentation of critical elements such as eligibility criteria. Monitoring is required at the following timepoints (but may be done more frequently):*<br>• *study initiation*<br>• *at least every six months while participants are receiving intervention and*<br>• *annually while participants are in follow-up*<br><br>External monitoring for the TLC trial will be performed by IND2Results, a CRO. IND2Results will draft an independent monitoring plan. | *At a minimum, a review is required annually when no one has been enrolled or the study is in long term follow up. Additional risk-based interim monitoring may be required at least once every 12-24 weeks based on the site activity, to include the possibility of remote monitoring. A longer frequency could be acceptable with justification about risk to participants.*<br><br>The IND2Results monitoring plan, at minimum, will include monitoring after the first participant is enrolled, every six months while participants are receiving intervention and annually while participants are in follow-up. | *Delegate a responsible party for each requirement below.* Self-assessment is acceptable.*<br>*Self-assessment*: a process for self-assessment of protocol compliance and data integrity which can be part of an overall DSMP. SeeEmory's self-assessment tool on this page.<br><br>Site monitoring by external monitor(s) will be performed by IND2Results according to the |

| | | | |
|---|---|---|---|
| | | | monitoring plan. |
| Real-time review of participant data during initial data collection. | To ensure that all pertinent data is accurately captured, real-time review will help prevent items from being overlooked. | *Expectation is that this happens every time you obtain information.* | *Everyone on the study team responsible for primary data collection.* |
| 100% review of regulatory files | To ensure that the regulatory file is current and complete for this study, and contains all of the necessary regulatory documents, from study start-up, to study completion. | *Reviewed at a minimum of first and close-out visits*<br><br>Review can occur more frequently if there is increased activity (modifications/amendments, revised protocols, revised consent forms, annual renewal submissions, reportable events submissions, etc.). | PI, Study Coordinator, External Monitor(s) from IND2Results |
| 100% review of consent forms | To ensure that participants are enrolled with the most current version of the consent form and that all consent forms are filled out completely. | Consent forms will be reviewed according to IND2Results' monitoring plan, at a minimum:<br>- after the first participant is enrolled<br>- six months after the first participant is enrolled<br>- every 12 months thereafter<br>- at the end of the study | PI and Lead Study Coordinator will review after each visit to obtain consent. External Monitor(s) from IND2Results will also review consent |

| | | | |
|---|---|---|---|
| | | | forms according to the monitoring plan. |
| Review of credentials, training records, the delegation of responsibility logs (if applicable) | To ensure that all study team members have completed the necessary onboarding/training requirements to begin working on this study and to ensure that study-specific responsibilities are captured for each team member | Review will take place at a minimum of study initiation and at study close-out, however, review may occur if new team members are added to the study staff roster. | Study Coordinator, External monitor(s) from IND2Results |
| Comparison of case report forms (CRF) to source documentation for accuracy and completion | To ensure that source data/information has been captured and transcribed accurately to case report forms/REDCap. | Review will take place at a minimum of study initiation and at study close-out; however, review may occur if new versions of CRFs are released. | Study Coordinator, External Monitor(s) from IND2Results |
| Review of documentation of all adverse events | To ensure that Adverse Events are captured and reported in a timely manner. | Adverse Events will be reviewed by study staff at the following timepoints:<br>- Individual adverse events will be reviewed in real-time<br>- An aggregate of adverse events will be reviewed each week<br>All study drop-outs and protocol deviations/violations will be reviewed each month. They will be reviewed by external CRO monitor per the monitoring plan. | PI, Study Coordinators, and CRO Study Monitor(s) |

| | | | |
|---|---|---|---|
| Monitoring of critical data points (eligibility, study endpoints, etc.) | To ensure complete documentation of critical elements such as eligibility criteria being met, and objectives being achieved | Critical data points will be reviewed according to IND2Results' monitoring plan, at a minimum:<br>- after the first participant is enrolled<br>- six months after the first participant is enrolled<br>- every 12 months thereafter<br>- at the end of the study | PI, Study Coordinator, and CRO Study Monitor(s) |
| Laboratory review of processing and storage of specimens | **Not Applicable**—No prospective labs are being collected in this study | **N/A** *Reviewed at first and close-out visits and at least biannually* | **N/A** |
| Assessment of laboratory specimens stored locally | **Not Applicable**—No prospective labs are being collected in this study; thus, there will no laboratory specimens stored locally | **N/A** | **N/A** |
| Test article accountability review | To maintain strict control over investigational drugs to ensure that the test article is used only for subjects enrolled in the study. | *Reviewed at first and close-out visits and at least biannually* | PI, IDS, CRO Study Monitor(s) |
| Accountability logs, dispensing records, and other participant records | To ensure that all IP dispensing counts are in alignment with number of enrollees. | Reviewed at first and close-out visits and *at least biannually*<br>PI will decide if pacing of review needs to be adjusted. | PI, CRC, Pharmacist, CRO Study Monitor(s) |
| **For FDA regulated studies, the following requirements apply:** | **How this Requirement is Met** | **Timing, frequency, and intensity of monitoring** | **Responsible Party(ies)** |

| | | | |
|---|---|---|---|
| Monitoring methods (may include centralized, on-site, and self-assessment) | To ensure this study is being conducted in accordance within the scope of institutional and federal regulations. | Monitoring for this study will be an ongoing and continual process. Monitoring for this fully decentralized trial will be done remotely by contracted CRO monitor(s) according to the monitoring plan | External Monitor(s) from IND2Results |
| *For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations. | | | |

**AE/SAE attributes will include:**

- Start and stop dates
- Severity
    - Severity will be reported in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v.5
    - If an appropriate listing is not present in this table for an AE, the AE will be graded as follows:
        - Grade 1 (Mild) – No interference with daily activity
        - Grade 2 (Moderate) – Some interference with daily activity but medical intervention not required (e.g., doctor visit and/or prescription medicine); over the counter medicine permitted
        - Grade 3 (Severe) – Prevents daily activity and requires medical intervention (e.g., doctor visit and/or prescription medicine)

- Causality/ relationship to IP—Causality assessment is required for AEs (and SAEs) that occur during clinical investigations. There is currently no standard international nomenclature to describe the degree of causality or relatedness of an AE with the IP. The following terms will be used during this study:
    - Likely – Reasons to consider an AE likely related to treatment may include, but are not limited to the following:
        - Timing of the event relative to the administration of the IP
        - Location of the AE relative to the site of IP administration
        - Likelihood based on experience with similar products
        - There is a biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
        - The AE is repeated on subsequent treatments

        - No other explanation is likely
    - Unlikely – An AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions, or subject's known clinical state.

A qualified study monitor will conduct remote risk-based monitoring of the trial to ensure that the study is conducted in accordance with the study protocol, ICH GCP E6, and FDA regulatory requirements. At the monitor's discretion, a random sampling of subjects may undergo full evaluation and comparison of source documentation with data entered into the study database.

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

The Investigator and the head of the medical institution, if applicable, agrees to allow the monitors direct access to all study-related documents.

**Language for Reporting as a Sponsor**

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

## 22. Provisions to Protect the Privacy Interest of Participants

### 22.1 Protection of Privacy

The electronic consent process and any televisits will take place using the secure and HIPAA compliant Emory Zoom and Emory's Part 11 compliant REDCap instance. Whether televisit or telephone call, study staff will ensure the potential subject is in a location with their desired level of privacy prior to beginning the visit. If the results of the study are published, the subject's identity will remain confidential.

Participants enrolled in the trial are made aware during the informed consent procedure that study personnel will be required to access the study subject's private medical records for trial conduct, and consent to this access prior to agreeing to participate.

### 22.2 Access to Participants

Conduct of the study and determination of feasibility of methods and procedures and safety evaluations of the intervention require access to the study subject's 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.

## 23. Economic Burden to Participants

There will be no costs to the participant for participating in this study. Participants will not be charged for any of the research activities. Any IP that is required during the trial will be provided free of charge. If the medication results in an AE or if study procedures result in any medical complications, the cost of treatment for those complications may be charged to the participant or their insurer. In the event of non-related AEs, the cost will be paid by the participant or their insurer.

## 24. Informed Consent

To preliminarily determine whether an interested party may be a candidate for this study, delegated research staff will obtain verbal consent and conduct a screening interview using a standardized pre-screen questionnaire. The verbal consent will describe the information to be collected during the screening interview and explain what will be done with the collected information. The pre-screen questionnaire will permit the study team to apply inclusion/exclusion criteria at a high-level to eliminate clearly ineligible candidates.

Written informed consent will be obtained by delegated research staff before beginning any study procedures. The consent conversation will be conducted remotely with the ICF presented to the participant as an electronic document (eConsent) through Emory's Part 11 compliant REDCap instance.

The entire informed consent form (ICF) will be reviewed with potential study subjects including all study procedures and expectations, risks, benefits, and what volunteering means. Participants will be asked questions to gauge their level of understanding. Potential participants will be given time to read the ICF and ask questions. If a potential participant

needs additional time to review the ICF or discuss study participation with family/friends, study staff will accommodate by scheduling a follow-up informed consent visit.

The PI may delegate qualified non-licensed study staff to obtain informed consent. If potential subjects have a medical-related question outside of the delegated person's scope of practice, or request to speak directly with a licensed person, the non-licensed staff member will contact the PI or any SIs. If the PI/SI are not available, study staff will accommodate by scheduling a follow-up informed consent visit.

- Non-English-Speaking participants will not be enrolled in this pilot study. Costs for translation of study documents and interpreters are prohibitive for the small budget of this pilot trial.
- Subjects who are not yet adults will not be enrolled in this study.
- Cognitively impaired adults will not be enrolled in this study.
    - Study Coordinators may assess potential subjects for decisional capacity; however, the PI is responsible for the ultimate determination as to an individual's capacity for consent.
- Adults unable to provide their own consent will not be enrolled in this study.

**25. Setting**

As this is a decentralized study all study-related visits and interactions will occur remotely.

Informed consent and televisits will take place using Emory University's Part 11 compliant instance of REDCap and Zoom platforms.

PI operates out of [redacted]

**26. Resources Available**

- Based on the current epidemiology, the duration of recruitment should be approximately four (4) months from first subject enrolled.
- Emory University and the U.S. Food and Drug Administration (FDA), in conjunction with the Critical Path Institute's CURE Drug Repurposing Collaboratory (C-Path/CDRC), for the purposes of Office of the Assistant Secretary for Planning and Evaluation (ASPE) are collaborating in the design and conduct of a platform randomized trial infrastructure. (Prime Grant Number: 2U18FD005320)
    - C-Path/CDRC will serve as the administrative coordinating center
    - C-Path/CDRC is providing a dedicated employee (CRC IV) for trial coordination and management.

    - The PI and CRC will be responsible for screening, enrollment, randomization, and physician confirmation of eligibility criteria on study participants, obtain baseline study data, and follow patients prospectively at 6, 9, 12 weeks with electronic patient reported outcomes (ePROs) per study protocol
- There are no anticipated consequences of the human research for which participants might need medical or psychological resources.
    - Subjects will be advised that if they are injured or get sick, they should go to the emergency room or other urgent care provider, as well as call the study doctor immediately.
- All study personnel will be trained on the protocol, have current certificates documenting GCP training and human subjects research ethics training, and receive documented delegation of authority for study tasks. Monitors will evaluate study team members to ensure access is consistent with training and delegation of authority logs.

## 27. References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## 28. Protocol Checklist

**Please note that protocol sections with an asterisk (*) should always be included in the protocol; if the section does not have an asterisk, and you have not included the section in the protocol, the IRB will consider it your attestation that the section does not apply to your study.**

| Protocol Section | Added to the protocol? |
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| **External Collaborators**- if applicable, add each external collaborator information and indicate whether that institution's IRB will review (or has already reviewed) that individual's engagement in human participants research activities) | ☒ **Yes** |
| **Funding Source***: Include the information for the funding entity for this study. Please explain if this study is covered by a sub-award or other pertinent information. Say "department" if you do not have any other funding. | ☒ **Yes** |
| **Objectives*:** Describe the purpose, specific aims, or objectives and state the hypotheses to be tested | ☒ **Yes** |
| **Background*:** Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Provide the scientific or scholarly background for, the rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge | ☒ **Yes** |
| **Study Endpoints*:** Describe the primary and secondary study endpoints. Describe any primary or secondary safety endpoints. | ☒ **Yes** |
| **Study Intervention/Investigational Agent*:** Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated. | ☒ **Yes** |
| **Drug/Device Handling:** If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on participants and be used only by authorized investigators.<br>If using a drug, explain if the control of the drug is managed by IDS (or VA/Grady/CHOA research pharmacies). If not, provide IDS exemption document.<br>If a device, explain how the device is being stored and managed. | ☒ **Yes** |
| If the drug is under an FDA REMS, plan to complete the REMS checklist found here, on the IRB website. | ☒ **Yes** |

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| If the drug is considered a controlled substance, make sure you have filled out this form. | ☒ **Yes** |
| If applicable, identify the holder of the IND/IDE/Abbreviated IDE. An Emory investigator who holds an IND or IDE is considered to be a Sponsor-Investigator (S-I). If the study is under an S-I, review this section of our website for additional requirements. | ☒ **Yes** |
| **Procedures involved***: Describe and explain the study design and include a study schema. Describe all research procedures being performed and when they are performed, including procedures being performed to monitor participants for safety or minimize risks | ☒ **Yes** |
| **Procedures-Minimizing risk*:** describe the procedures performed to lessen the probability or magnitude of risks. | ☒ **Yes** |
| **Procedures- Drug/Device Use:** describe all drugs and devices used in the research and the purpose of their use and their regulatory approval status | ☒ **Yes** |
| **Procedures-Source Records*:** describe source records that will be used to collect data about participants. Attach all surveys, scripts, and data collection forms to the submission. | ☒ **Yes** |
| **Procedures-Data collection*:** describe what data will be collected during the study and how that data will be obtained | ☒ **Yes** |
| **Procedures- Long Term Follow Up*:** once all research-related procedures are complete, what data will be collected during this period. If no data is collected after procedures are completed, please state in the submission. | ☒ **Yes** |
| **Data and Specimen Banking:** describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens. Depending on the volume and nature of the collection, this may require a separate repository-specific IRB submission. The VA Data Repository SOP is required if the study is creating a data repository at the Atlanta VA.<br>List the data to be stored or associated with each specimen.<br>Describe the procedures to release data or specimens, including the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens. | ☒ **Yes** |

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| **Sharing of Results with Participants*:** Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant's primary care physicians) and if so, describe how the results will be shared If applicable (e.g. for studies involving scans and/or panels of exploratory testing on specimens)<br>Plan for managing the types of findings that might arise. This should include any secondary findings that are being sought actively, findings that might be anticipatable, and findings that might be un-anticipatable.<br>Plan for recognizing, analyzing, and handling incidental findings and how incidental findings will be communicated to participants during the consent process. If the plan is not to disclose any findings, then this should be included. This plan might include the option for participants to opt-out of receiving incidental findings.<br>Description of the research team's responsibilities following disclosure of a finding. This should detail educational information about the nature of the finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required.<br>Reminder to include language in the consent form to let the participants know your plans for this – see Modular Language for Informed Consent Forms on IRB website) | ☒ **Yes** |
| **Study timelines*:** describe the duration of an individual participant's participation in the study; anticipated time to enroll all study participants and the estimated date for the investigators to complete this study (complete primary analyses) | ☒ **Yes** |
| **Inclusion and Exclusion Criteria*:** describe how individuals will be screened for eligibility and the criteria that define who will be included or excluded in your final study sample | ☒ **Yes** |
| **Population*:** describe the study population and indicate specifically whether you will include or exclude each of the following special populations:<br>• Adults unable to consent<br>• Individuals who are not yet adults (infants, children, teenagers)<br>• Pregnant women<br>• Prisoners<br><br>Note: you cannot exclude people with limited English proficiency unless you can demonstrate the scientific need for such exclusion.<br>Community Participation: For studies aimed at addressing issues that affect a certain community or group: How, if at all, will this study involve people from the target community | ☒ **Yes** |

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| in the design of the study? Conduct of the study? How will the results of the research be shared with the participants and/or the target community/ies?<br><br>**If studying Race or Ethnicity, have you defined these terms, and explained their proposed mechanism of action if these characteristics will be used in an explanatory model?** | |
| **Research with pregnant women, fetuses, or neonates:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research with neonates of uncertain viability:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving prisoners:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving children:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving cognitively impaired adults:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving economically or educationally disadvantaged persons:** describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects | ☒ **Yes** |
| **Local Number of Participants*:** Indicate the total number of participants to be accrued locally. If applicable, distinguish between the number of participants who are expected to be enrolled and screened, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.)<br>Provide your projected enrolling goals, including the percentage of participants according to sex and race. | ☒ **Yes** |
| **Recruitment Methods*:** Describe when, where, and how potential participants will be recruited. Describe the source of participants. Describe the methods that will be used to | ☒ **Yes** |

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| identify potential participants. Describe materials that will be used to recruit participants. Attach copies of these documents with the application.<br>If including advertisements, attach the final copy of them. When advertisements are taped for broadcast*, attach the final* audio/videotape. You may submit the wording of the advertisement before taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/videotape. Describe the amount and timing of any payments to participants. Reimbursement for expenses/travel?<br>If using contests or raffles as incentive, you must offer entry to all potential participants, not just those who enroll in the study/complete study-related procedures, per Georgia State Law.<br>All research recruitment through social media needs to follow this guidance, which does not allow the use of personal social media accounts for some recruitment activities. | |
| **Withdrawal of Participants*:** Describe anticipated circumstances under which participants will be withdrawn from the research without their consent. Describe any procedures for orderly termination. Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection. | ☒ **Yes** |
| **Risk to Participants*:** List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related to the participant's participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.<br>If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable.<br>If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.<br>If applicable, describe risks to others who are not participants. | ☒ **Yes** |
| **Potential Benefits to Participants*:** Describe the potential benefits that individual participants may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include benefits to society or others. | ☒ **Yes** |
| **Compensation to Participants*:** Describe if/how subjects will be compensated for participation in this study. Indicate what method compensation will be delivered (e.g. cash, gift card, school credit). Describe the amount and timing of any payments to participants. | ☒ **Yes** |

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| How much? What kind? Is tax information required? (if so, must be reflected in the informed consent form). Will payments be pro-rated if a participant withdraws early? | |
| **Data Management and Confidentiality*:** Describe the data analysis plan, including any statistical procedures or power analysis. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission. Describe any procedures that will be used for the quality control of collected data. | ☒ **Yes** |
| **Describe how data or specimens will be handled study-wide*:** What information will be included in that data or associated with the specimens?<br>• Where and how data or specimens will be stored?<br>• How long the data or specimens will be stored?<br>• Who will have access to the data or specimens?<br>• Who is responsible for receipt or transmission of the data or specimens?<br>• How data or specimens will be transported? | ☒ **Yes** |
| **Data Monitoring and Participants Safety (if this study is more than minimal risk, this section is required):**<br>Ensure that you review our Data and Safety Monitoring plan guidance for specific details about this section, and examples of what the IRB will be requiring according to the level of risk.<br>If a DSMB is needed, please describe the composition of the board (if not already detailed in the protocol). Review this guidance for more information. If the sponsor protocol does not contain all required information, please in this section.<br>Describe the plan to periodically monitor the data at the site level according to risk level. Include the appropriate completed monitoring table, if applicable.<br>Description of the plan for notifying the IRB of reportable events, whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them.<br>Please address the specific details below. If deemed not applicable, please provide rationale: | ☒ **Yes** |

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| Subject safety:<br>• Specific subject safety parameters<br>• Frequency of subject safety observations<br>• Individual responsible for safety monitoring<br>• Subject stopping rules – under what conditions will a subject be removed from study participation and who will make the decision?<br>• Study stopping rules - under what conditions will the study be modified or stopped and who will make the decision?<br>• Reporting mechanisms (i.e. Deviations, adverse events, UPs)<br><br>Data Integrity:<br>• Specific data elements to be reviewed<br>• Frequency of monitoring data, points in time, or after a specific number of participants<br>• Individual responsible for data monitoring<br><br><u>Additional considerations for FDA regulated trials</u><br>Depending on the procedures affecting risks to participants, the site monitoring plan should specify:<br>• Categorization of activities done centrally and those on-site if applicable<br>• Monitoring methods (may include centralized/remote, on-site, and self-monitoring)<br>• Reference to any tools used (i.e. checklists)<br>• Identification of events that may trigger changes<br>• Identification of deviations or failures that would be critical to study integrity | |
| **Provisions to Protect the Privacy Interests of Participants*:** | **☒ Yes** |
| • Describe the steps that will be taken to protect participants' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information.<br>• Describe what steps you will take to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of | |

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| intrusiveness a participant might experience in response to questions, examinations, and procedures.<br>• Indicate how the research team is permitted to access any sources of information about the participants. | |
| **Economic Burden to Participants*:** Describe any costs that participants may be responsible for because of participation in the research. | ☒ **Yes** |
| **Consent Process*:** Describe where the consent process will take place, any waiting period available between informing the prospective subject and obtaining the consent; and the process to ensure ongoing consent.<br>Describe the role of the individuals listed in the application as being involved in the consent process; the time that will be devoted to the consent discussion; steps that will be taken to minimize the possibility of coercion or undue influence; and steps that will be taken to ensure the participants' understanding.<br>**Note**: If you are planning to obtain consent via electronic signature, please review this document. Additional guidance on consent documentation and process can be found on our website, under the consent toolkit. | ☒ **Yes** |
| **Consent Process-Non-English-Speaking Participants*:**<br>Indicate what language(s) other than English are understood by prospective participants or representatives.<br>If participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those participants will be in that language.<br>Indicate the language that will be used by those obtaining consent.<br>If you checked N/A, please provide reasoning of why subjects with limited English proficiency are excluded.<br>**Note**: if you stated that subjects with LEP will be enrolled, you are approved for the use of the Emory IRB short forms. Please read the guidance about the use of short forms here. | ☒ **Yes** |
| **Consent Process-Children:** After determining if the subject is a child per GA law (or if enrolled outside GA, per state/country law), please describe whether parental permission will be obtained from: | ☒ **Yes** |
| • Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. | |

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| • One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.<br><br>Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.<br><br>When assent of children is obtained describe whether and how it will be documented per Emory Policies and Procedures | |
| **Consent Process-Cognitively Impaired Adults:** describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require children to sign assent documents. | **☒ Yes** |
| **Consent Process-Adults Unable to Consent:** List the individuals from whom permission will be obtained in the order of priority. (E.g., durable power of attorney for health care, a court-appointed guardian for health care decisions, spouse, and adult child.)<br>For research conducted in the state, review "46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT" to be aware of which individuals in the state meet the definition of "legally authorized representative."<br>For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research.<br>Describe the process for the assent of the participants. Indicate whether:<br><br>• Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not.<br>• If assent will not be obtained from some or all participants, an explanation of why not.<br><br>Describe whether the assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require participants to sign assent documents | **☒ Yes** |
| **Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)** | **☒ Yes** |

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| Review the Emory IRB waiver document to ensure you have provided sufficient information for the IRB to make these determinations.<br>If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. | |
| **Setting*:** Describe the sites or locations where your research team will conduct the research including where the subject will be identified and recruited, where the research procedures will be performed, and if you will involve a community advisory board. For research conducted outside the organization and its affiliates describe the site-specific regulations or customs affecting the research outside the organization and the local scientific and ethical review structure outside the organization. | ☒ **Yes** |
| **Resources Available*:** Describe the resources available to conduct the research such us the feasibility of recruiting the required number of suitable participants within the agreed recruitment period; describe the time that you will devote to conducting and completing the research; describe the availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research; describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions. | ☒ **Yes** |
| **Multi-Site Research when Emory is the Lead Site:**<br>Study -Wide Number of Participants: indicate the total number of participants to be accrued across all sites.<br>Study-Wide Recruitment Methods: If this is a multicenter study and participants will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.<br>Describe when, where, and how potential participants will be recruited.<br>Describe the methods that will be used to identify potential participants.<br>Describe materials that will be used to recruit participants.<br>Describe the processes to ensure communication among sites. See "WORKSHEET: Communication and Responsibilities (HRP-830)." All sites have the most current version of the protocol, consent document, and HIPAA authorization.<br>All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).<br>All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented. | ☒ **Yes** |

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| All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.<br>All local site investigators conduct the study in accordance with applicable federal regulations and local laws.<br>All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy<br>Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"): | |
| • Problems (inclusive of reportable events).<br>• Interim results.<br>• The closure of a study | |
| If this is a multicenter study where you are a participating site/investigator, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).") | |
| • Where and how data or specimens will be stored locally?<br>• How long the data or specimens will be stored locally?<br>• Who will have access to the data or specimens locally?<br>• Who is responsible for receipt or transmission of the data or specimens locally?<br>• How data and specimens will be transported locally? | |