Complete Research Protocol (HRP-503)

Table of Contents

Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

Response Example
Intervention Group:
Control Group:

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response: A pilot placebo-controlled randomized double-blind trial of Melatonin in outpatients with COVID infection.

PRINCIPAL INVESTIGATOR:

Name
Department
Telephone Number
Email Address

Response: Co-PIs

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Department: Medicine
Telephone Number: (716) 888-4864
E-Mail: ssethi@buffalo.edu

VERSION NUMBER/DATE:

Include the version number and date of this protocol.

Response: 01-23-2021, version 8

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
8/4/2020	2		yes
9/24/2020	3	1. Addition of adverse events of special interest (depression and anxiety: addition of GAD-2 and PHQ-2 questionnaires; and drowsiness: will be monitored by coordinator at visits, severity and timing will be recorded) 2. Patient symptom logs will be collected through day 42 instead of through Day 15 3. Addition of external reviewer for outcomes, adverse events, SAEs to determine if drug or disease related. He	yes

		will also if hospitalizations are COVID related. External reviewer is Tom Russo MD. He has been added to study team. 4. Inclusion criteria: Must include emergency contact 5. Exclusion criteria: define liver disorders specifically, was included prior but they wanted specific definitions 6. Added Collection of WHO Clinical Progression Scale (0-10) through electronic medical records	
11/2/2020	4	Addition of protein to sample analysis	
11/5/2020	5	Added + test within 72 hrs in inclusion criteria, It was orginially supposed to be there but was left out of this section.	
11/16/2020	6	Changed courier deliver window from 15 and 42 days to 15 ± 3 and 42 ± 3 days	
01/05/2021	7	Increased time of symptoms and positive test to within 5 days to increase enrollment	
01/15/2021	8	Addition of rapid antigen test for screening. Addition of social media advertising and other forms of advertising for recruitment. Addition of payment $50 per subject. Updated risks of Nasopharyngeal swabs.	

FUNDING:

Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.

Response: SUNY SEED

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: SUNY SEED

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response: All study approval documents and correspondence that is not stored in the Click System will be retained in the office of Dr. Margarita Dubocovich.

Location: Jacobs School of Medicine and Biomedical Science, Suite 3212

Address: 955 Main Street, Buffalo, NY 14203

Department: Pharmacology and Toxicology

1.0 Study Summary

Study Title	A pilot placebo-controlled randomized double-blind trial of Melatonin in outpatients with COVID infection.
Study Design	This study is a pilot randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of melatonin in outpatient adult patients suspected to be afflicted with COVID-19.
Primary Objective	Evaluate the safety of the intervention through 42 days of follow-up as compared to the control arm as assessed by: • Cumulative incidence of serious adverse events (SAEs) • Cumulative incidence of Grade 3 and 4 adverse events (AEs). • Adverse Events of Special Interest • Discontinuation or temporary suspension of the investigational medication (for any reason).
Secondary Objective(s)	Evaluate the clinical efficacy of melatonin as compared to placebo as assessed by: **Hospitalization** Incidence of COVID related hospitalization at 42 days. Data will be obtained from electronic medical record. **COVID related symptoms** The speed of resolution of COVID related symptoms Change from baseline Day 1 to Day 42. Change in the WHO Clinical Progression Scale (0-10). Data will be obtained from electronic medical record. **Mortality** 42-day mortality. Data will be obtained from electronic medical record.

Research Intervention(s)/ Investigational Agent(s)	Melatonin (5-methoxy-N-acetyl tryptamine)
IND/IDE #	150700
Study Population	Outpatient adult (≥18 years old) patients with COVID-19.
Sample Size	30 subjects
Study Duration for individual participants	42 days
Study Specific Abbreviations/ Definitions	COVID-19: Coronavirus Disease 2019

2.0 Objectives*

2.1 Describe the purpose, specific aims, or objectives of this research.

Response: The study is designed to evaluate the safety and efficacy of Melatonin. Participants will be enrolled as outpatients within 5 days of positive COVID-19 test. The ultimate goal is to determine in an adequately powered study if the anti-inflammatory and antioxidant actions of Melatonin can reduce the severity and prevent progression of COVID when started in mild disease.

2.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response: Melatonin reduces inflammation and oxidative stress in COVID-19 patients reducing the severity of the disease.

3.0 Scientific Endpoints*

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

*NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should **not** be a date.*

Response:

Primary Objective

Evaluate the safety of the intervention through 42 days of follow-up as compared to the control arm as assessed by:

- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of Grade 3 and 4 adverse events (AEs).

- Adverse Events of Special Interest
- Discontinuation or temporary suspension of the investigational medication (for any reason).

Secondary Objectives

Evaluate the clinical efficacy of melatonin as compared to placebo as assessed by:

Hospitalization: Incidence of COVID related hospitalization at 42 days. Data will be obtained from electronic medical record.

COVID related symptoms: Fever, chills, cough, nasal symptoms, body aches/muscle aches, headache, loss of smell, loss of taste, nausea, vomiting, diarrhea, fatigue, dizziness. The speed of resolution of COVID related symptoms. Change from baseline, Day 1 to Day 42. Accessed by questionarre.

Change in the WHO Clinical Progression Scale (0-10). Data will be obtained from electronic medical record.

Mortality: 42-day mortality. Data will be obtained from electronic medical record.

Exploratory Objective

Evaluate the effect of melatonin on virologic parameters as compared to placebo and assessed by:

-Percent of subjects with SARS-CoV-2 detectable in saliva sample at days 1, 3, 7, 14, 28 and 42.

-Quantitative RT-PCR for SARS-CoV-2 virus in saliva sample at days 1, 3, 7, 14, 28 and 42.

-Evaluate the reduction in cytokine/chemokine RNA and/or protein levels in saliva:

-Reduction as compared to baseline (Day 1) in salivary levels of cytokine/chemokine RNA and/or protein (IL-1, Il-2, IL-3, IL-4, IL-6, IL-8, IL-10, IL-11, IL-12, IL-13, Il-17, IL-18, TNFα, IFNy, IFNα, IFN-B, MCP1) at days 3, 7, 14, and 28.

4.0 Background*

4.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response: Overproduction of cytokines and chemokines is believed to contribute to the development in COVID-19 disease (Zhang et al. 2020; Law et al. 2005; Cheung et al. 2005). Studies have shown in the blood of patients with COVID-19 there was a marked increase in the cytokines and chemokines interleukin 1β (IL-1β). interferon-γ (IFN-γ), interferon-inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1) and interleukin-4 (IL-4) (Huang et al. 2020; Zhang et al. 2020). Currently, the overall cumulative hospitalization rate is 20.0

per 100,000, with the highest rates in persons 65 years and older (63.8 per 100,000) and 50-64 years (32.8 per 100,000) (CDC 2020). Therefore, the majority of COVID-19 positive patients are not hospitalized and may have a milder course of disease. Consequently, methods that reduce the increase in cytokines that may result in severe course of disease, is necessary.

Melatonin, a pineal hormone, has been shown to have anti-inflammation, anti-oxidation and immune enhancing features (Andersen, et al. 2016). In multiple animal models of sepsis, acute lung injury, allergic asthma, respiratory syncytial virus (RSV) induced oxidative pulmonary injury, and ventilator-induced lung injury, melatonin supplementation has been shown to decrease the number of inflammatory cells, reduce the levels of the cytokines IL-4, IL-5, IL-13 and TNF-a and reduce nitric oxide and hydroxyl radical concentrations (Peng et al. 2018; Shin et al. 2014; Pedreira et al. 2008; Kim et al. 2012; Wu et al. 2012; Wang et al. 2018; Zhao et al. 2018; Aliasgharzadeh et al. 2019; Wu et al. 2020; Shang et al. 2009; Chen et al. 2011). In a randomized controlled trial, 8-week oral intake of 6 mg/d melatonin caused a significant decrease in serum levels of IL-6, TNF-α and C-reactive protein in subjects with diabetes mellitus and periodontitis (Bazyar et al. 2019). A significant decrease in TNF-α, IL-1b, IL-6, lipoperoxides and levels of nitric oxide catabolites occurred following oral administration of 25 mg/day melatonin for 6 months in subjects patients suffering from relapsing-remitting multiple sclerosis (Sanchez-Lopez et al. 2018). A meta-analysis of 22 randomized controlled trials indicates that melatonin supplementation significantly reduces the levels of TNF-α and IL-6 (Bazyar et al. 2019). Melatonin increases the proliferation and maturation of natural killer cells and other immune cells (Miller et al. 2006). This evidence supports the use of melatonin as a supplement to reduce the levels of cytokines in COVID-19 patients (Zhang et al., 2020*).*

4.2 Include complete citations or references.

Response:

Aliasgharzadeh, A., B. Farhood, P. Amini, H. Saffar, E. Motevaseli, S. Rezapoor, F. Nouruzi, D. H. Shabeeb, A. Eleojo Musa, M. Mohseni, H. Moradi, and M. Najafi. 2019. 'Melatonin Attenuates Upregulation of Duox1 and Duox2 and Protects against Lung Injury following Chest Irradiation in Rats', Cell J, 21: 236-42.

Andersen, L. P., I. Gogenur, J. Rosenberg and R. J. Reiter (2016). "The Safety of Melatonin in Humans." Clin Drug Investig 36(3): 169-175.

Bazyar, H., H. Gholinezhad, L. Moradi, P. Salehi, F. Abadi, M. Ravanbakhsh, and A. Zare Javid. 2019. 'The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: a double-blind, placebo-controlled trial', Inflammopharmacology, 27: 67-76.

CDC. 2020. 'Coronavirus Disease 2019 (COVID-19)'. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

Chen, C. F., D. Wang, R. J. Reiter, and D. Y. Yeh. 2011. 'Oral melatonin attenuates lung inflammation and airway hyperreactivity induced by inhalation of aerosolized pancreatic fluid in rats', J Pineal Res, 50: 46-53.

Cheung, C. Y., L. L. Poon, I. H. Ng, W. Luk, S. F. Sia, M. H. Wu, K. H. Chan, K. Y. Yuen, S. Gordon, Y. Guan, and J. S. Peiris. 2005. 'Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis', J Virol, 79: 7819-26.

Huang, C., Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, and B. Cao. 2020. 'Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China', Lancet, 395: 497-506.

Kim, J. Y., Y. D. Lee, B. J. Kim, S. P. Kim, D. H. Kim, K. J. Jo, S. K. Lee, K. H. Lee, and H. W. Baik. 2012. 'Melatonin improves inflammatory cytokine profiles in lung inflammation associated with sleep deprivation', Mol Med Rep, 5: 1281-4.

Law, H. K., C. Y. Cheung, H. Y. Ng, S. F. Sia, Y. O. Chan, W. Luk, J. M. Nicholls, J. S. Peiris, and Y. L. Lau. 2005. 'Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells', Blood, 106: 2366-74.

Pedreira, P. R., E. Garcia-Prieto, D. Parra, A. Astudillo, E. Diaz, F. Taboada, and G. M. Albaiceta. 2008. 'Effects of melatonin in an experimental model of ventilator-induced lung injury', Am J Physiol Lung Cell Mol Physiol, 295: L820-7.

Peng, Z., W. Zhang, J. Qiao, and B. He. 2018. 'Melatonin attenuates airway inflammation via SIRT1 dependent inhibition of NLRP3 inflammasome and IL-1beta in rats with COPD', Int Immunopharmacol, 62: 23-28.

Sanchez-Lopez, A. L., G. G. Ortiz, F. P. Pacheco-Moises, M. A. Mireles-Ramirez, O. K. Bitzer-Quintero, D. L. C. Delgado-Lara, L. J. Ramirez-Jirano, and I. E. Velazquez-Brizuela. 2018. 'Efficacy of Melatonin on Serum Pro-inflammatory Cytokines and Oxidative Stress Markers in Relapsing Remitting Multiple Sclerosis', Arch Med Res, 49: 391-98.

Shang Y, Xu SP, Wu Y, Jiang YX, Wu ZY, Yuan SY, Yao SL. 2009. 'Melatonin reduces acute lung injury in endotoxemic rats.', Chin Med J (Engl). 122: 1388-93.

Shin, I. S., J. W. Park, N. R. Shin, C. M. Jeon, O. K. Kwon, J. S. Kim, J. C. Kim, S. R. Oh, and K. S. Ahn. 2014. 'Melatonin reduces airway inflammation in ovalbumin-induced asthma', Immunobiology, 219: 901-8.

Wang, S., Z. Zhao, X. Feng, Z. Cheng, Z. Xiong, T. Wang, J. Lin, M. Zhang, J. Hu, Y. Fan, R. J. Reiter, H. Wang, and D. Sun. 2018. 'Melatonin activates Parkin translocation and rescues the impaired mitophagy activity of diabetic cardiomyopathy through Mst1 inhibition', J Cell Mol Med, 22: 5132-44.

Wu, G. C., C. K. Peng, W. I. Liao, H. P. Pao, K. L. Huang, and S. J. Chu. 2020. 'Melatonin receptor agonist protects against acute lung injury induced by ventilator through up-regulation of IL-10 production', Respir Res, 21: 65.

Wu, W. S., M. T. Chou, C. M. Chao, C. K. Chang, M. T. Lin, and C. P. Chang. 2012. 'Melatonin reduces acute lung inflammation, edema, and hemorrhage in heatstroke rats', Acta Pharmacol Sin, 33: 775-82.

Zhao, X., J. Sun, W. Su, H. Shan, B. Zhang, Y. Wang, A. Shabanova, H. Shan, and H. Liang. 2018. 'Melatonin Protects against Lung Fibrosis by Regulating the Hippo/YAP Pathway', Int J Mol Sci, 19.

Zhang, R., X. Wang, L. Ni, X. Di, B. Ma, S. Niu, C. Liu, and R. J. Reiter. 2020. 'COVID-19: Melatonin as a potential adjuvant treatment', Life Sci, 250: 117583.

5.0 Study Design*

5.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: placebo-controlled randomized double-blind pilot trial

6.0 Study Intervention/Investigational Agent

1.1 Description: *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

Response: Melatonin (5-methoxy-N-acetyl tryptamine)

6.1 Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response:

Melatonin is a synthetic product with white physical appearance. Melatonin is sold as a food supplement for use in humans. This study will use Melatonin Tables (10 mg per capsules) purchased from Life Extension (Northeast Fulfillment, Inc, Edison, NJ 08837) (see certificate of analysis attached) and shipped directly to research pharmacist and stored in the research pharmacy in the CRC.

Melatonin will be administered as a 10 mg dose three times a day for 14 days. Capsules (size "4" Clear Vegetable cellulose capsule with off-white fill) containing 10 mg melatonin, microcrystalline cellulose, and rice concentrate prepared by Life Extension® (Northeast Fulfillment, Inc, Edison, NJ 08837) will be over-encapsulated in opaque gelatin capsules. Placebo capsules will be prepared with identical opaque gelatin capsules using methylcellulose. Both melatonin and placebo capsules will be given orally. Over-encapsulation of placebo and melatonin treatments will be done by the research pharmacist and will be mailed to study subjects directly by courier.

Melatonin capsules will be stored at room temperature.
Placebo capsules will be stored at room temperature.

6.2 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: IND approved

7.0 Local Number of Subjects

7.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: 30

7.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response: 60

7.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: There are approximately 50 to 100 + COVID results reported daily in Erie County. In addition, many more individuals with COVID symptoms do not get tested. In order to to facilitate enrollment and determination of subject eligibility, those with symptoms of COVID-19 within 5 days that have not received a test or its result will be given a rapid antigen test to confirm eligibility for the study.

8.0 Inclusion and Exclusion Criteria*

*8.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

a. Male or non-pregnant female adult ≥18 years of age at time of enrolment.
b. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study.
c. Onset of COVID-19 Symptoms within 5 days
d. Positive testing for COVID-19 infection by standard RT-PCR assay or equivalent test within 5 days or willingness to receive a rapid antigen test (EUA Nasal swab antigen test) by the study team. Follwing enrollment, among subjects that have not recieved a COVID test yet or its results, a nasopharyngeal swab sample will be obtained and a rapid antigen test **(CareStart™ COVID-19 Antigen Test)** by the studyteam.
e. Meets criteria for mild or moderate COVID disease defined as follows:
   Mild COVID-19
   • Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
   • No clinical signs indicative of Moderate, Severe, or Critical Severity
   Moderate COVID-19
   • Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
   • Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute.
   • No clinical signs indicative of Severe or Critical Illness Severity
f. Subject provides written informed consent prior to initiation of any study procedures.
g. Understands and agrees to comply with planned study procedures.
h. Agrees to the collection and storage of saliva samples per protocol.
i. Subject agrees to provide an emergency contact who the study team can contact in case the subject is not reachable on any of the study visits

*8.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

a. Severe chronic kidney disease (eGFR<30 ml/min) or Moderate renal impairment (eGFR 30-60 ml/min) or requiring dialysis
b. Severe hepatic insufficiency defined as one or more of the following: Cirrhosis diagnosis, Serum ALT > 3x ULN or Alkaline phosphatase >3x ULN or bilirubin >2x ULN in the absence of Gilbert's or hemolysis, Uncontrolled acute or chronic liver disease (e.g. acute hepatitis A, unstable autoimmune hepatitis)
c. Pregnancy or breast feeding.
d. History of a seizure disorder.
e. Patient is taking Fluvoxamine, Capmatinib, Ciprofloxacin (Systemic),

Deferasirox, Givosiran, Methoxsalen (Systemic), Mexiletine, Rucaparib, Stiripentol, Thiabendazole, Vemurafenib, Methoxsalen, Sodium oxybate or Echinacea.

f. Allergy to the study medication
g. Currently taking melatonin
h. Currently taking high dose (>500 mg/day) Vitamin C.
i. Meets criteria for Severe or Critical COVID-19 infection defined as follows:

Severe COVID-19

• Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress

• Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300

• No criteria for Critical Severity

Critical Covid-19

• Evidence of critical illness, defined by at least one of the following:

– Respiratory failure defined based on resource utilization requiring at least one of the following:

- Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

– Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors)

– Multi-organ dysfunction/failure

8.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

8.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

*In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may **not** be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: Because of the pilot nature of this proposal with limited funding, we are not including non-English speaking individuals. However, if this pilot project leads to a larger study, such subjects will be included.

9.0 Vulnerable Populations*

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

*9.1 For research that involves **pregnant women,** safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

☒ **N/A**: This research does not involve pregnant women.

*9.2 For research that involves **neonates of uncertain viability or non-viable neonates,** safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

*9.3 For research that involves **prisoners**, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

*9.4 For research that involves **persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")**, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

*9.5 For research that involves **cognitively impaired adults**, safeguards include:*
NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

*9.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response: Not applicable as no population will be specifically targeted.

10.0 Eligibility Screening*

*10.1 Describe **screening procedures** for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

📎 *Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).*

Response: Patients that have COVID-19 Symptoms within 5 days will be assessed for eligibility. All screening procedures will take place entirely remotely by phone. Screening will begin with a brief presentation about the study followed by a screening checklist. We will rely on patient's statements over the phone to ensure they meet inclusion and exclusion criteria. Individuals who meet the inclusion and exclusion criteria and are interested in participating in the study will then proceed to providing informed consent at the in person visit. Once consented, a subject that has not had a COVID-19 test will be given a rapid antigen test. This test is done on a nasopharyngeal swab sample. Those that test positive will continue in the study; those who test negative we be removed from the study.

☐ **N/A:** There is no screening as part of this protocol.

11.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that

all records review procedures and inclusion/exclusion screening are adequately described in other sections.

11.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response:

It is anticipated that patients with COVID-19 will call their primary care physicians or present to emergency rooms. Recruitment efforts will include dissemination of information about this trial to these health care providers. We will be sending a flyer for recruitment (submitted) to primary care practices, emergency rooms and urgent care centers in the area, such as UBMD primary care practices and Kaleida and ECMC emergency rooms. The health care practitioners will provide potential participants the contact information for study staff. Only potential participants who then contact the study staff will be enrolled in this study.

We will be working with the Clinical and Translational Science Institute (CTSI) Community Engagement Team (CET) to create awareness of the study through their professional and community contacts. The tools they have available may include the Buffalo Research Registry (BRR, IRB Approved STUDY00000806), the Patient Voices Network (PVN), the Conventus CTSI/PVN and Evergreen Research Tables, and conducting outreach at various community events. These tools are methods by which the CET distributes IRB-approved recruitment information to community members.

We will also utilize the services of The CTSI Community Engagement Team (CET) to assist in participant recruitment.

BUFFALO RESEARCH REGISTRY

The Clinical and Translational Science Institute's (CTSI) Community Engagement Team (CET) hosts the Buffalo Research Registry (BRR, IRB Approved STUDY00000806), a resource that connects researchers looking to recruit participants and community members looking to get involved with research. To participate in the registry, volunteers complete a voluntary intake form.

Volunteers have agreed to be contacted about potential research opportunities based on their self-reported information.

As described in the BRR's IRB Approved Protocol (STUDY00000806), key personnel from the CTSI will serve as the conduit between our research team and the registry volunteers. Key personnel will verify our IRB study approval, review inclusion and exclusion criteria and will sort the registry data accordingly.

In terms of recruiting for our study, key personnel will pull volunteer reports using the inclusion and exclusion criteria. Key personnel will centrally invite volunteers to participate in the study and provide a warm hand off to our team.
There are two ways we may share our study. These include:
1. Electronically- Using the volunteer report from REDCap, key personnel from the CTSI will send initial e-mail invites to introduce our study to registry volunteers.
2. Post Mail- Key personnel from the CTSI will provide our team with contact information (i.e. first name, last name, post mail address) to prepare a mailing. This information will be shared in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail.

We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed. We also plan on conducting follow-up by phone/email after initial contact. This contact information will be provided in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail. We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed. We will have no access to the health information provided in the registry.
The CET hosts the Buffalo Research Registry (BRR, IRB Approved STUDY00000806), a voluntary registry which can connect us to community members who have completed a health profile and are interested in participating in research. These community members have agreed to be contacted about potential research opportunities based on their self-reported information.
COMMUNITY OUTREACH AND TABLING
The CET also tables at many events in the community throughout the year and may display the IRB approved flyer for this project at their table at community events. Examples of events the CET attends include Good for the Neighborhood hosted by Independent Health Foundation, UB on the Green, Juneteenth, Elmwood Arts Festival and many others.

The CET also hosts standing tables at the Conventus Building on the 4th floor of UBMD and at Evergreen where the IRB approved flyer can be made available to community members and patients. This will occur only after agreement between the CET and UBMD Conventus and/or Evergreen partners that the study is appropriate for the venue.

Social Media Recruitment Plan

This study will be shared via the social media platform Facebook. At this time no paid ads will be placed. A member of the study team member will contact social media managers and group/page administrators to request they post our Facebook post content to their public Facebook pages or private groups.

11.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: Prospective subjects control their own privacy interests as they will contact the research team if interested in participation. Prospective subjects will be interviewed over the phone where the interviewer will be in a private room.

11.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response: We will be sending a flyer for recruitment to primary care practices, emergency rooms and urgent care centers in the area. The same flyer will be posted on social media. A telephone script will be used when the participant calls the research team to introduce the study. Both are submitted.

12.0 Procedures Involved*

*12.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response: Because of the highly contagious nature of COVID infection in the first few days after onset of symptoms, it is essential to minimize exposure of research team members to the subjects. Therefore, except for the enrollment visit, all procedures for this study will be conducted remotely at the subject's home. The Table below depicts all the research procedures.

	Screen	***Enrollment***							
Day +/- Window	**−1 or 1**	**1**	**Daily until**	**Daily until**	**Day 3 ± 1**	**Day 7 ± 1**	**Day 14 ± 2**	**Day 28 ± 3**	**Day 42 ± 3**

			day 14	day 42					
Assessments/Procedures									
ELIGIBILTY									
Informed consent	X								
Demographics & Medical History	X								
Prior SARS-CoV-2 based on screening or perform rapid antigen testing	X								
STUDY INTERVENTION									
Randomization		X							
Administration of Melatonin/Placebo		X	X						
STUDY PROCEDURES									
Body temperature		X	X	X	X	X	X	X	X
Clinical data collection		X	X	X	X	X	X	X	X
Pulse Oximetry measurement		X	X	X	X	X	X	X	X
Adverse event evaluation		X			X	X	X	X	X
RESEARCH LABORATORY									
Saliva for PCR SARS-CoV-2		X			X	X	X	X	X
Saliva for Cytokine/Chemokine RNA and/or protein		X			X	X	X	X	X

Below is a day by day description of the study procedures.

- For those subjects that have not had a COVID-test: Subjects will be enrolled and then tested for SARS-CoV2 using an EUA rapid antigen administered by the study team. If negative by rapid antigen test subjects will be withdrawn from study. Those subjects that have a prior positive test will not be give a rapid antigen test.
- If COVID-19 positive:
- Collect a baseline sample of saliva prior to taking drug, by spitting in a collection container that will be provided at time of consent.
- Rate COVID symptoms before starting medication and then each day in the evening on a short questionnaire from Day 1 to Day 42.
- Record body temperature and pulse oximetry each day in the morning and evening.
- Take the IP 3 times a day orally for 14 days.
- On Days 3, 7, 14, 28 and 42 collect a sample of saliva prior to taking drug in a collection container provided. Place the sample in a collection bag and place it in a freezer.
- Speak to the research coordinator through telemedicine on Days 3, 7, 14, 28 and 42 to provide

data as well as any adverse effects of the treatment. These include anxiety and depression and drowsiness special interest adverse events. The duration of these visits will be 15-30 minutes.

- Allow a courier to come to your house to collect study related materials on Day 15 ± 3 and day 43 ± 3 to pick up study related materials.

12.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response: Please see Table above

12.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response: Included documents: 1) Data collection form (baseline); 2) Data collection form (Follow-up); 3) Daily symptom questionnaire; 4) Body temperature and pulse oximetry logs; 5) Instructions for saliva collection, storage and shipping 6) WHO Clinical Progression Scale

12.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: EMR data will be accessed to ascertain baseline health information and information relevant to the participants COVID illness. The study team will have remote access to the relevant EMRs.

*12.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: No

*12.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: Study results will be posted on Clinical Trials.gov and submitted for publication in a peer reviewed journal.

13.0 Study Timelines*

13.1 Describe the anticipated duration needed to enroll all study subjects.

Response:

2 to 4 months

13.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: An individual subject will complete the study in about 42 days, from screening and enrollment at day -1 or 1 to follow-up on day 42 ± 3 days. After enrollment, there are a total of 5 telemedicine study visits. Each will last approximately 15-30 minutes.

13.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response:

Up to 6 months

14.0 Setting

14.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response: Because of the highly contagious nature of COVID infection in the first few days after onset of symptoms, it is essential to minimize exposure of research team members to the subjects. Therefore, except for the enrollment visit, all procedures for this study will be conducted remotely at the subject's home. The interviewer will maintain privacy and security by ensuring their conversation cannot be overhead and that all study related documents are stored in a password protected folder with access limited to study personnel. The IP and matching placebo will be stored and distributed from the Research Pharmacy at the CRC. Study packages that contain daily symptom questionnaire, daily temperature and pulse oximetry logs, a thermometer, a pulse oximeter, saliva collection kits and return packaging will be assembled in the CRC by the research coordinator and be given to subject at the time of consent. We anticipate 2 courier visits to the participant's homes. On Day 15-17 to pick up saliva samples and questionnaires and unused IP and then on Day 29-31 to pick up the last saliva sample and unused study materials.

14.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response: NA

☐ **N/A:** This study is not conducted outside of UB or its affiliates.

15.0 Community-Based Participatory Research

15.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response: NA

☐ **N/A:** This study does not utilize CBPR.

15.2 Describe the composition and involvement of a community advisory board.

Response: NA

☐ **N/A:** This study does not have a community advisory board.

16.0 Resources and Qualifications

*16.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response:

Co-PI: Margarita L. Dubocovich, PhD is a SUNY Distinguished Professor in the Department of Pharmacology and Toxicology in Jacobs

School of Medicine and Biomedical Sciences. She is also Senior Associate Dean for Diversity and Inclusion. She has over 30 years of experience studying melatonin and melatonin receptors.

Co-PI*:* Sanjay Sethi MD, is a Professor of Medicine and Chief of the Division or Pulmonary and Critical Care Medicine in Jacobs School of Medicine and Biomedical Sciences. He is also the Medical Director of the Clinical Research Office. He has expertise in pulmonary diseases including chronic obstructive pulmonary disease (COPD).

Co-I: Gregory Wilding PhD is the Professor and Chair of the Department of Biostatistics in the School of Public Health and Health Professions (SPHHP). He has expertise in the design and analysis of clinical studies and have participated in many aspects of clinical and non-clinical research.

Co-I: Jessica L. Reynolds PhD is an Associate Professor of Medicine in Jacobs School of Medicine and Biomedical Sciences. She has expertise in Immunology and Infectious Disease.

External Reviewer: Thomas Russo MD, an infectious disease specialist at University of Buffalo will serve as an external reviewer for the outcomes collected in this study. Specifically, he will adjudicate whether the adverse events (grade 3 or 4) and SAEs collected are drug or disease related. He will also adjudicate whether the hospitalizations observed in this study were COVID related or not. These adjudications will be on blinded data.

Research Pharmacist: Denise Swiatek PharmD is the designated research pharmacist at the Clinical Research Center in the UB CTRC building.

Research Coordinator: To be hired.

Describe other resources available to conduct the research.

16.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response:

Margarita L. Dubocovich, PhD 0.05 FTE

Sanjay Sethi MD 0.05 FTE

Gregory Wilding PhD 0.05 FTE

Jessica L. Reynolds PhD 0.05 FTE

Thomas Russo MD 0.05 FTE

16.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: If a research staff determines that the participant needs additional medical or psychological resources during the course of the study, they will ask the participant to contact their primary care practitioner in non-emergent situation or to go the Emergency Department in emergent situations.

16.4 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.

Response: The co-PIs of this study will assign the research team members the research related duties and ensure that they are adequately trained to perform the duties. Any amendments to the study protocol and any events that alter the risk-benefit ratio of the study will be promptly communicated to the team members.

17.0 Other Approvals

17.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response:

Prospective subjects will be interviewed over the phone where the interviewer will be in a private room. Subjects will be at their residence or place of work.

18.2 Indicate how the research team is permitted to access any sources of information about the subjects.

*NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question **does apply** to records reviews.*

Response: HIPAA waiver. Consent of the participants.

19.0 Data Management and Analysis*

19.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response:

Randomization: Participants will be randomized to the intervention or control arm in a 2:1 fashion using a permuted block randomization scheme. The randomization lists to be used in this study will be generated by the study biostatistician. Subjects will be included in data analyses according to their randomized assignment irrespective of the treatment actually received (intent-to-treat).

Missing data: The amount and nature of missing data will be characterized and no method of imputation will be used for missing data. We acknowledge the possibility of informative missingness with some of the outcomes, that is, the probability of a particular observation being missing may be related to the health or death of a subject, and therefore analyses will be interpreted with caution.

Accrual: Participants will be accrued to the study on a first-come basis. The projected accrual is approximately 15 per month, and therefore recruitment is expected to be complete at most 60 days following the study starting point. Subjects will be followed for 1 month after recruitment completion, so total study duration will be approximately 3 months. During the enrollment period, the study biostatistician will model and predict accrual rates in order to verify adequacy of the enrollment process.

Descriptive analyses: Measured outcome variables will be summarized overall and by relevant demographic and baseline variables. Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data, ex., histograms, boxplots, scatterplots, etc.

Statistical analyses: Analyses will be performed with a focus on estimation of specific clinically important parameters, including preliminary evidence of safety and activity of the intervention, for use in the planning of subsequent comparative trials designed to fully assess safety and efficacy. The primary outcomes in the examination of the study intervention, specifically, the cumulative incidence of serious adverse events (SAEs), the cumulative incidence of Grade 3 and 4 adverse events (AEs), and the discontinuation or temporary suspension of the investigational medication (for any reason), are measured in a binary fashion at the

study participant-level. The corresponding probabilities will each be estimated using the relative frequency. In addition to the point estimates based on collected data, 95% confidence intervals will also be computed based on the methodology of Clopper and Pearson. Additional binary study outcomes, ex., incidence of COVID-related hospitalization and hospitalization for any reason, will be analyzed in an identical fashion. Comparison between randomized groups with regards to these outcomes will be done using Fisher's exact test. For numeric outcomes, such as symptom questionnaire results and measures of clinical improvement, the rank-based Wilcox rank sum test will be used to compare groups. For outcomes which may be subject to censoring such as speed of resolution of COVID related symptoms, parameter estimation will be based on the Kaplan-Meier estimator and the log-rank test will be utilized to compare groups, Proposed exploratory outcomes are collected longitudinally. Proposed exploratory outcomes are collected longitudinally. Standard statistical techniques for the analysis of such outcomes, ex., mixed linear models, will be utilized. Although primary analyses will be performed based on the intent-to-treat principle, to evaluate the robustness of these results, analyses will also be conducted in a secondary fashion based on actual treatment received. All statistical tests will be two-sided and tested at a 0.05 nominal significance level. All analyses will be carried out using SAS version 9.4 (or higher) statistical software (Cary, NC).

19.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response:

Sample size justification: In that accurate assessment of the safety of the study intervention is of utmost importance in this study, the samples size of 20 in the intervention group is based on the expected precision associated with our estimated safety probabilities corresponding to the primary outcomes expressed in terms of confidence interval width. Note that a true probability of 0.5 represents the mathematically worst-case scenario with in regards to precision and therefore we may take precision at that point to be an upper bound of expected accuracy. We see that with a sample size of 20 participants the standard error of these estimators will be at most 11 percentage points.

19.3 Describe any procedures that will be used for quality control of collected data.

Response: Collected data will be reviewed by the co-PIs on a weekly basis to ensure adequate data collection.

20.0 Confidentiality*

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*20.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response:

Identifiers will be collected on the Demographics page of the Baseline form. This form will be kept in a locked cabinet in the PI's office. This form will contain the Study subject ID number and their initials. All subsequent forms will only contain the Subject Study ID number and their initials.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet in the PIs office. Electronic files will be password protected.

Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, Sponsor and the pertinent regulatory authorities.

20.2 A. How long will the data be stored?

Response: Data will be stored for the duration of this study and up to ten years after procurement.

20.3 A. Who will have access to the data?

Response: Only members of the PI's research team will have access to the data obtained from participants. De-identified data will be made available to the broader scientific public per FDA policy.

20.4 A. Who is responsible for receipt or transmission of the data?

Response: The co-PIs are responsible.

20.5 A. How will the data be transported?

Response: The paper data collection forms will be transported by the research personnel in subject specific manila folders to the PIs office where they will be stored under lock and key.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

20.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: Specimens will be stored in -80°C freezers in the laboratory of the Co-I in the Clinical and Translational Research Center where access is restricted to building employees only. Specimens labels will only have the study subject number and therefore will be coded.

20.7 B. How long will the specimens be stored?

Response: All coded specimens will be stored for the duration of this study and up to ten years after procurement.

20.8 B. Who will have access to the specimens?

Response: Only members of the PI's research team will have access to the specimens obtained from participants.

20.9 B. Who is responsible for receipt or transmission of the specimens?

Response: Saliva specimens collected up to Day 28 will be transported by courier to the CTRC and received by Dr. Reynolds, the co-I.

20.10 B. How will the specimens be transported?

Response:

Saliva Specimens will be transported from the subject's home to the CTRC by Courier. The subject will be instructed to place the collected saliva specimens in a biohazard bag and then store them in their home refrigerator/freezer. The specimens will be provided to the courier who will bring them to the laboratory in a thermacol box that contains ice pack or dry ice.

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

21.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: On a weekly basis the co-PIs will review the data being collected to determine if there are any worrisome patterns of the adverse events (grade 3 or 4) and SAEs reported. This review will be blinded. We do anticipate a 20% rate of hospitalization in our subjects. Therefore, only if the rate is much higher than that will there be a cause of concern.

21.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: All safety data will be reviewed.

External Review of Data

Thomas Russo MD, an infectious disease specialist at University of Buffalo will serve as an external reviewer for the outcomes collected in this study. Specifically, he will adjudicate whether the adverse events (grade 3 or 4) and SAEs collected are drug or disease related. He will also adjudicate whether the hospitalizations observed in this study were COVID related or not. These adjudications will be on blinded data.

21.3 Describe any safety endpoints.

- Response: Cumulative incidence of serious adverse events (SAEs)
  - Cumulative incidence of Grade 3 and 4 adverse events (AEs).
  - Adverse effects of special interest: Anxiety and Depression (GAD-2 and PHQ-2 questionnaires); Drowsiness (will be recorded)
  - Discontinuation or temporary suspension of the investigational medication (for any reason).

21.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: The safety information will be collected by scheduled phone calls as described above.

21.5 Describe the frequency of safety data collection.

Response: Days 1, 3, 7, 14, 28 and 42

21.6 Describe who will review the safety data.

Response: The co-PIs will review the data along with the biostatistician Dr. Wilding.

21.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: Weekly

21.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: As the number of participants is small and data is blinded, formal statistical testing will not be used.

21.9 Describe any conditions that trigger an immediate suspension of the research.

Response: A hospitalization rate that is much larger than the anticipated 20%. A high incidence of adverse events that can be potentially attributed to Melatonin.

22.0 Withdrawal of Subjects*

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*22.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: If they have adverse events that could be possibly related to Melatonin such that the study team think their continued participation is not advisable. If participants are noncompliant with the research procedures, there is the possibility they will be withdrawn from the research.

For those subjects that have not had a previous tests, once enrolled if the subject is found to be COVID-19 negative by EUA rapid antigen testing, the subject will be withdrawn from the study.

22.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: An end of study visit will be conducted over the phone and a courier will be sent to pick up study materials and samples.

22.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: Subjects who withdraw from taking the study drug will be encouraged to stay in the study. If they choose not to, a telephonic end of study visit and courier collection of samples and study materials will be done. Already collected data and samples will not be removed from the study database.

23.0 Risks to Subjects*

23.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response:

Nasopharyngeal swabs are associated with discomfort that is usually short-lived.

Potential risks associated with the use of planned doses of melatonin include dizziness, headache, vivid dreams, nausea and sleepiness, that are anticipated to be of mild severity.

Breach of confidentiality is an associated risk of this research.

23.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: The frequent telephonic follow-up and the availability of the study team to the participants in case adverse effects arise.

Please see section 20.1 for procedures performed to lessen the risk of breach of confidentiality.

*23.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: Melatonin has never been studied in COVID patients, therefore there are unforeseeable risks.

23.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: Melatonin has not been studied in pregnancy.

23.5 If applicable, describe risks to others who are not subjects.

Response: NA

24.0 Potential Benefits to Subjects*

24.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response:

The candidate therapeutic(s) being evaluated may or may not improve clinical outcome of an individual adult subject with COVID-19 who participates in this trial. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agents under study as well as the natural history of the disease. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

The overall risk of using Melatonin in COVID is likely to be low and the potential benefit is high. This favorable risk-benefit ratio supports the conduct of this pilot study, and if the results of this pilot study are consistent with our expectations, a larger definitive trial.

25.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*25.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: There is no available compensation to subjects for research related injury.

25.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: There will be no compensation for research related injuries.

26.0 Economic Burden to Subjects

26.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: None

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

27.0 Compensation for Participation

27.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: Subjects will receive a one time payment of $50 for participation on completion of the study.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☒ **N/A:** There is no compensation for participation. This section does not apply.

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*

☐ ***No*** *(If no, Skip to Section 27.0)*

28.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response:

The consent process could take place at the ED or physician's office, or at a COVID research clinic location on Maple road in Amherst under development. The person obtaining the consent will do so from a private room to ensure their conversation is not overheard.

28.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: At the time of the enrollment interview, the consent will be reviewed and discussed with the subject and all pertinent questions answered. Following the interview process, the subject will be offered additional time to decide if they want to participate.

28.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response:

The subject will be informed as part of the consent process that they can withdraw from the study at any time.

28.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are 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*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☐ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

28.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response: NA

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response: NA

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 26.9)

28.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

28.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

28.10 ***For research conducted outside of New York 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 research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: NA

28.11 Describe the process for ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects.* ***If some, indicate which adults will be required to assent and which will not.***

Response:

- ***If assent will not be obtained from some or all subjects, provide an explanation of why not.***

Response:

28.12 Describe whether ***assent of the adult*** *subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

*28.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response:

*28.14**For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

28.15 Describe whether parental permission will be obtained from:

Response:

☐ 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.

☐ 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.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

*28.16Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

*28.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

28.18 When assent of children is obtained, describe how it will be documented.

Response:

29.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

29.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

29.2 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. Provide any additional information necessary here:

Response:

30.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

30.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the

requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

31.0 Multi-Site Research (Multisite/Multicenter Only)*

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

31.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

*31.2 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as the following. See "WORKSHEET: Communication and Responsibilities (HRP-830).":*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately in accordance with applicable federal regulations and local laws.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

31.3 Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):

- *Problems (inclusive of reportable events)*
- *Interim results*
- *Study closure*

Response:

*31.4 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?*
- *How long the data or specimens will be stored locally?*
- *Who will have access to the data or specimens locally?*
- *Who is responsible for receipt or transmission of the data or specimens locally?*
- *How data and specimens will be transported locally?*

Response:

31.5 If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described elsewhere in the protocol.

- *Describe when, where, and how potential subjects will be recruited.*
- *Describe the methods that will be used to identify potential subjects.*
- *Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response:

32.0 Banking Data or Specimens for Future Use*

☒ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*32.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response:

32.2 List the data to be stored or associated with each specimen.

Response:

32.3 Describe the procedures to release banked data or specimens for future uses, 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.

Response: