RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED PROOF-OF-CONCEPT TRIAL OF RESVERATROL FOR THE OUTPATIENT TREATMENT OF MILD CORONAVIRUS DISEASE (COVID-19)

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Principal Investigator: Marvin R McCreary, MD
IND/IDE Sponsor: Marvin R McCreary, MD
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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED PROOF-OF-CONCEPT TRIAL OF RESVERATROL FOR THE OUTPATIENT TREATMENT OF MILD CORONAVIRUS DISEASE (COVID-19)	
Study Description:	Proof of concept trial to determine the safety and explore the efficacy of using resveratrol and vitamin D3 to treat patients with mild COVID-19	
Objectives:	Primary Objective:	To compare the 21-day hospitalization rate among early or mild stage COVID-19 patients taking a 15-day regimen of resveratrol pus vitamin D3 to that for patients taking an identical placebo regimen.
	Secondary Objectives:	Decrease morbidity and mortality in terms of reduced days of symptoms, reduced rate of ICU admission, reduced rate of mechanical ventilation, and reduced mortality.
Endpoints:	Primary Endpoint:	Hospitalization rate
	Secondary Endpoints:	ICU Admission rate, invasive ventilation rates, duration of symptoms, and mortality rates.
Study Population:	200 hundred patients (100 per group) 45 years and older who test positive for SARS-COV2 who have mild COVID-19 based on WHO Baseline Severity Categorization	
Phase:	2	
Description of Sites/Facilities Enrolling Participants:	Outpatients presenting to COVID-19 testing sites of Mt Carmel Health Systems in Columbus, OH, which may include drive-thru testing centers, emergency departments, urgent care centers.	
Description of Study Intervention:	Patients will be placed on a 15-day course of two 500 mg resveratrol capsules 4 times per day, versus the same dosing frequency of placebo. Both groups will receive 100,000 IU on day one only.	
Study Duration:	up to 6 months	
Participant Duration:	60 days	

1.2 SCHEMA

Prior to Enrollment Screening

- Total n=200
- Review electronic report of newly positive SARS-CoV2 test results of patients 45 and older
- If old records are available, clinicians to prescreen for exclusion criteria
- Contact potenially eligible participants by phone to discuss interest in study
- Patient referred to an online site to review a video discribing the study, risk, benefits.
- Patient given the opportunity to ask questions
- Obtain informed consent electronically
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Randomization

- Intervention Group 1 (n=100)
- Placebo (n=100)

Day1 Baseline Survey & Start treatment

- Patient take Vitamin D3 100,000 IU on day and starts treatment or placebo
- Patients will receive an baseline assessment using Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™).

Day 2-15 Treatment or placebo and daily online survey

- Participant to take 2 capsules of intervention or placebo 4 times per day for 15 days.
- Participant will receive a daily online survey to assess for signs and symptoms of COVID-19 and to report potential side effects. If a patient has not completed an online survey within 24 hours, the patient will be contacted via phone to check their status.

Day 8, 15, 21 Weekly PRO-CTCAE Survey

- Patients will questionnaire with 7 day look back of adverse events based on the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™).

Between day 21-30 Follow-up assessments for efficacy

- Clinicians will perform a chart review to assess patient outcomes as well as contact patient for an exit interview via phone.

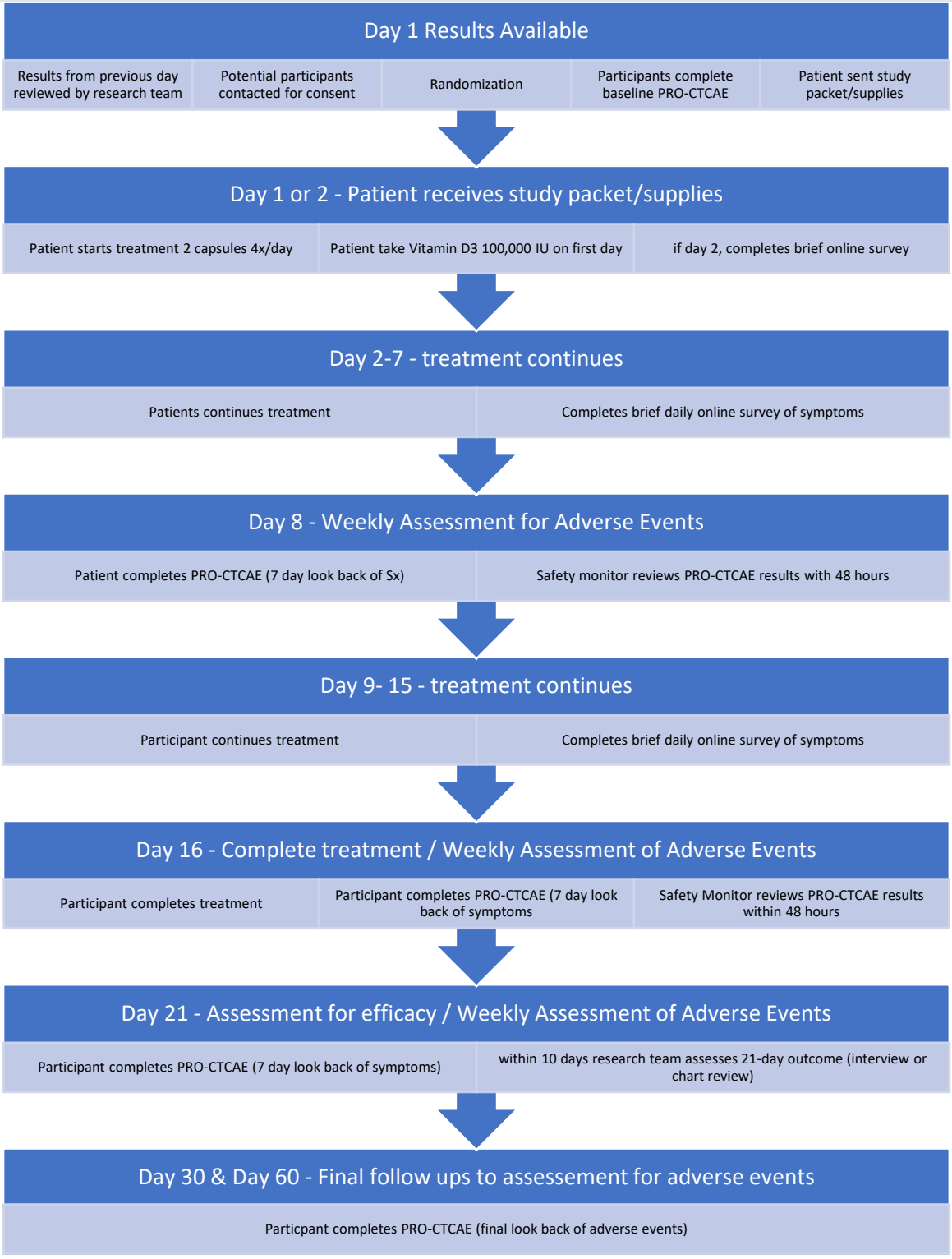
Day 30 and Day 60 Long term assesment

- Participant Completes PRO-CTCAE to evaluate for adverse events

Study Completion Follow-up assessments of study endpoints and safety

- Data analysis
- Possible long term follow up of adverse events as outlined in section 8.3

1.3 SCHEDULE OF ACTIVITIES (SOA)



2 INTRODUCTION

2.1 STUDY RATIONALE

Resveratrol (RV) is a polyphenol produced by plants in response to injury or infection. It is found in grapes, peanuts, and other common foods. RV has been associated with a variety positive health effects in areas of inflammation, cardiovascular diseases, cognitive disease, cancer, diabetes, and infectious disease (Tomé-Carneiro, et al., 2013) (specifically including viral diseases (Abba, Hassim, Hamzah, & Noordin, 2015)). RV is readily available commercially as a plant extract and can be produced by genetically engineered yeast (Li, et al., 2015). COVID-19 is the disease caused by a novel coronavirus (SARS-CoV2) that can result in life threatening complications, including lung injury and stroke. While there are numerous trials investigating treatment options, there are no proven effective treatment options. Multiple lines of preclinical data suggest that RV may be effective against coronavirus (See Figure 1).

2.2 BACKGROUND

Coronavirus (CoV) is characterized by surface spike proteins than bind to a region of the Angiotensin-converting enzyme 2 (ACE2) of the respiratory tract. Binding to the ACE2 is required for entry into the affected cell and is dependent upon a transmembrane serine protease (TMPRSS2) (Hoffmann, et al., 2020). After entry into the cell a variety of processes occur, including the down regulation of ACE2 (Kuba, et al., 2005) as well as the subsequent destruction of the pneumocyte. The deficiency in ACE2 caused by SARS is associated with lung injury (Yan, Xiao, & Lin, 2020). Damage to the pneumocyte triggers the release of inflammatory mediators, and the subsequent release of cytokines (IL1, IL6, TNF-α) and reactive oxygen species. While these effects are part of the host defense mechanism, the resultant inflammation is destructive to the alveoli. A “cytokine storm” results in further damage to the alveoli and the development of Acute Respiratory Distress Syndrome (ARDS) (Mehta, et al., 2020).

In addition to ACE2 being a binding site for CoV, it is also associated with protective effects in SARS induced lung injury (Nicholls & Peiris, 2005) (Gu, et al., 2016). ACE2 may attenuate vascular permeability, inflammatory cell infiltration, pulmonary edema, hyaline membrane formation, and prevent acute lung injury (Yan, Xiao, & Lin, 2020). RV has been shown to upregulate ACE2 (Moran, et al., 2017). The upregulation of ACE2 by RV may provide protective effects in COVID-19 (Imai, et al., 2005) (Yan, Xiao, & Lin, 2020) (Horne & Vohl, 2020) (Magrone, Magrone, & Jirillo, 2020).

RV’s antiviral, anti-inflammatory, and antioxidant properties may be helpful in reducing the clinical effects of COVID. (See Figure 1). RV has demonstrated antiviral effects in a variety of animal and human disease (Abba, Hassim, Hamzah, & Noordin, 2015). Specific to CoV, in vitro studies demonstrate that RV inhibits MERS-CoV infection by decreasing nucleocapsid protein resulting in reduced viral production and increased cell survival. (Lin, et al., 2017). Starting at the first steps in the infection *in silico* modeling suggests that RV may interfere with the binding of CoV spike protein to the ACE2 receptor (Wahedi, Ahmad , & Sajjad , 2020) (Rane, Chatterjee, Kumar, & Ray, 2020). RV has been shown to downregulate

TMPRSS2 (Wilson, et al., 2017). Noting that after CoV binds to ACE2, TMPRSS2 may be required to activate cell entry of CoV into the host cell (Shulla, et al., 2011), the downregulation of TMPRSS2 by RV could help reduce the infectivity of the virus. *In silco* analysis also suggests that resveratrol may inhibit COVID-19 RNA Dependent Polymerase and Papain-like Protease (El-Aziz, Shehata, Awad, & El-Sohaimy, 2020) (Ranjbar, Jamshidi, & Torabi, 2020) which could explain the inhibition of nucleocapsid protein described by Lin et al 2017. In silico analysis also demonstrates potential inhibition of the coronavirus main proteinase (Mpro) (Mishra, Pathak, & Tripathi, 2020) which would be additional mechanism of inhibiting viral replication.

Coronavirus is associated with the potential for excessive inflammation. CoV has been shown to activate Toll-Like Receptor 4 leading to an unbalanced inflammatory response and damaging inflammation (Olejnik, Hume, & Mühlberger, 2018). RV has been demonstrated to inhibit TLR4 activation (Sun, et al., 2018). CoV has been shown to increase pro-inflammatory cytokines IL-1, IL-6 (Conti, et al., 2020), CCL5 (RANTES) (Patterson, et al., 2020) and TNF-α (Wang, et al., 2007). Suppression of inflammation has been shown to be therapeutic in a variety of illnesses. RV has been shown to reduce inflammation via a variety of mechanisms (Zhu, Lei, & Dong, 2017) including decreasing the release of inflammatory cytokines in the macrophages of patients with COPD (Culpitt, et al., 2003). RV has also been shown to inhibit the proinflammatory transcription factor NF-κB (Ren, et al., 2013) and inhibition of NF-κB has been shown to increase survival in a mouse model of SARS-COV1 (DeDiego, et al., 2014). The anti-inflammatory effects of RV may be beneficial in mitigating the cytokine storm that is associated with ARDS and high mortality of COVID-19 (Mehta, et al., 2020).

Oxidant stress is associated with viral infections. Inflammatory cytokines trigger the release of reactive oxygen species (ROS). Excessive release of ROS damages both infected as well as healthy cells and may play a role in heart and lung tissue damage in COVID-19. The use of antioxidants has been proposed in the treatment of COVID-19 (Wang & Zhang, 2020). RV's antioxidant properties may provide additional outcome benefits.

Prevention of lung injury would be a main treatment goal in COVID-19. The cytokine storm associated is one of the main mechanisms on injury. Therefore, it is notable that a mouse model of cytokine storm showed a 100% mortality reduced to 0% in resveratrol treated mice with minimal lung injury in the treated group (Alghetaa, et al., 2018). Furthermore, the cytokine storm of COVID-19 leads to ARDS. A mouse model of ARDS uses lipopolysaccharide (LPS) as a model of ARDS caused by sepsis (Chen, Bai, & Wang, 2010). RV has demonstrated protective effects in LPS induced lung injury (Hu, Chen, Li, Jiang, & Zhu, 2019) (Jiang, et al., 2016). The proposal by Jaing is RV's inhibition of NLRP3 inflammasomes. Inhibition of NLRP3 inflammasomes in another proposed therapeutic target in COVID-19 (Shah, 2020) (Yap, Moriyama, & Iwasaki, 2020).

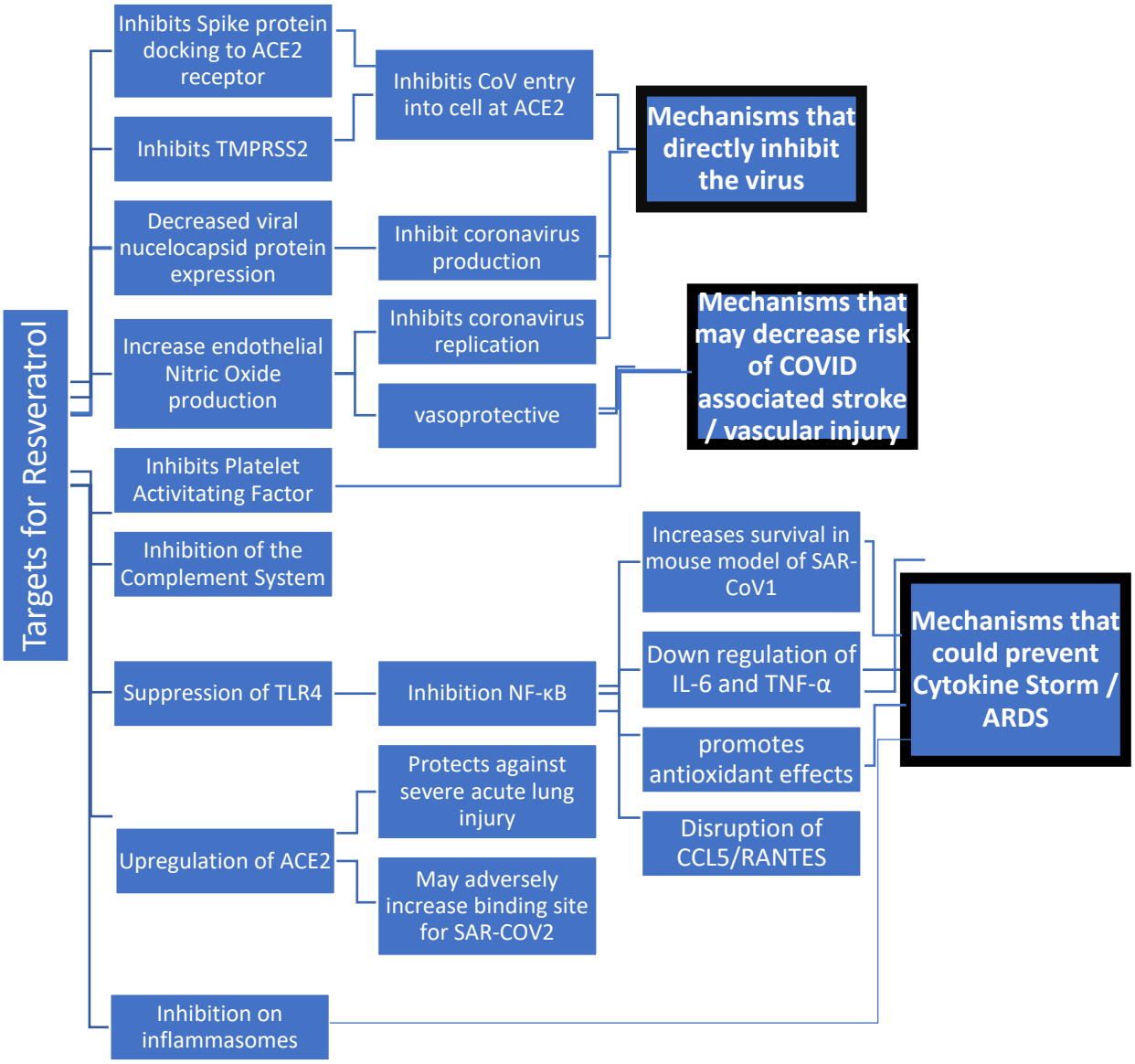
As the above discussion regarding RV's effects are largely based on in vitro models of disease, there is always a concern regarding whether in vitro models will translate into in vivo efficacy. Multiple animal studies have shown that RV does improve outcomes in animal models of viral infections. A porcine

model of pseudorabies virus shows that piglets inoculated with the virus had no mortality at an orally administered RV dose of 30mg/kg (a dose comparable to an easily achievable human dose) compared to a 40% mortality in the untreated group. Specifically, that study showed alveolar destruction in the untreated group vs mild lung injury in the treated group. The proposed mechanism is inhibition of IκB kinase (Zhao, et al., 2018). It is notable that a drug prediction analysis of SARS-CoV2 suggests that IκB kinase inhibition is a potential target for COVID-19 (Fagone, et al., 2020). Similarly, a murine model of H1N1 influenza showed dose dependent inhibition of viral replication and showed a 60% survival rate in RV treated mice compared to 20% in placebo treated mice (Palamara, et al., 2005). In Respiratory Syncytial Virus infected mice, RV treated mice showed significantly less lung damage compared to untreated mice (Zang, et al., 2011).

Recently, case reports have described an increased risk of stroke associated with COVID-19. This has been attributed to coronavirus attaching to ACE2 receptors of vascular endothelium leading to endothelial injury (Markus & Brainin, 2020) (Akshay Avula, 2020). Excessive complement activation has been proposed as an additional mechanism of thrombotic microangiopathy and complement inhibition has been proposed as an adjunctive treatment to decrease the severity of COVID-19 (Campbell & Kahwash, 2020). RV has been shown to inhibit complement activation in mice (Wu, et al., 2015). Activation of TLR4 by CoV may be the trigger associated with increased Platelet Activating Factor (PAF). RV has been show in inhibit PAF (Shigematsu, et al., 2003) which may be protective in the setting of cerebral ischemia (Lei, Tu, Wang, Tu, & Shi, 2019). RV has been associated with a variety vasoprotective effects (Das & Das, 2010) (Gracia-Sancho, Villarreal, Zhang, & García-Cardeña, 2010). One of the vasoprotective mechanisms reported is increased endothelial nitric oxide (Xia, Förstermann, & Li, 2014). Nitric oxide is an antioxidant and signaling molecule that has been shown to inhibit viral replication, viral protein synthesis, and viral RNA synthesis in SARS-CoV (Åkerström, et al., 2005) (Åkerström, Gunalan, Keng, Tan, & Mirazimi, 2009). These mechanisms may decrease the risk of stroke in COVID-19.

Given the scale of the health and economic impacts of COVID-19, any treatment that can reduce hospitalizations could have a significant impact in this pandemic. RV is generally recognized as safe and has been shown to have positive health benefits in human trials. Prior research in human trials related to lung disease, in vitro studies of RV for coronavirus, and animal studies of RV in other viral infections support investigating RV as a treatment for coronavirus disease (COVID-19) (see summary in Figure 1). Given that RV is readily available and could be cheaply scaled up through the fermentation of yeast, it is potentially a scalable solution to treat coronavirus disease.

2.2.1 FIGURE 1. – SUMMARY OF RESVERATROL EFFECTS ON VIRUS AND HOST



2.3 RISK/BENEFIT ASSESSMENT

2.3.1 SAFETY AND DRUG INTERACTIONS

To characterize toxicity, RV has been dosed at 200mg/kg/day in rats and 600mg/kg/day in dogs with no observed adverse effects (NOAEL) as measured by clinical observations, hematology, ophthalmology, cardiovascular, and neurotoxicity evaluation along with evaluation of organ weights, histopathology and gross pathology (Johnson, et al., 2011).

While human clinical trials have shown RV to generally be safe and well tolerated at doses of up to 5g, dose related gastrointestinal upset has been reported (Ramírez-Garza, et al., 2018). There are some additional concerns of adverse effects based primarily on in vitro studies and animal models (Shaito, et al., 2020). High doses are associated with inhibition of cytochrome P450 (specifically CYP3A4, CYP2D6, & CYP2C9), which could result in some drug interactions, most concerning for drugs with a narrow therapeutic window. Drug interactions with nicardipine, warfarin, HIV protease inhibitors, anti-arrhythmics, calcium cancel agonists, and antihistamines, and immunosuppressants have been reported in animal models (Shaito, et al., 2020). Hydroxychloroquine and chloroquine, drugs with narrow therapeutic window, are being investigated for use in COVID-19, are notably metabolized by CYP2C8 and CYP3A4. With the exception of a patient with multiple myeloma undergoing chemotherapy plus high dose RV who became dehydrated and developed renal failure (cast nephropathy), other studies of RV in humans have not shown adverse effects of hematologic, hepatic, thyroid, and renal functions (Tomé-Carneiro, et al., 2013).

Medication that have been reported in the literature as co-administered medications with resveratrol include amoxicillin, aspirin, atorvastatin, bortezomib, buspirone, caffeine, carbamazepine, cholinesterase inhibitors, dextromethorphan, DHA, EPA, epigallocatechin-3-gallate, inositol, hydroxychloroquine, glibenclamide, lactoferrin, losartan, meloxicam, memantine, metformin, methotrexate, N-acetylcysteine, orlistat, Pegylated-Interferon-α2b, piperine, prednisolone, PUFA, r-tPA (activase), Ribavirin, sulfasalazine, vitamin D3, as well as generic descriptions of the inclusion of “anti-hypertensive drugs,” “anti-thrombotics,” “beta-blockers,” “glucose-lowering drugs,” “statins,” “NSAIDS,” and patient’s “usual medications”.

Despite the extensive list of medications that have reportedly been co-administered with resveratrol there is little published information about reported adverse events/adverse interactions associated with these co-administered medications. There are multiple reports of benefits/synergistic effects. The 2 most useful references for adverse events and drug interactions are “Drug Interaction Potential of Resveratrol” (Detampel, Beck, Krähenbühl, & Huwyler, 2012) and “Potential Adverse Effects of Resveratrol: A Literature Review” (Shaito, et al., 2020). The source literature that is the basis of concern for CYP interactions is largely based on healthy volunteer studies in “Resveratrol Modulates Drug- and Carcinogen-Metabolizing Enzymes in a Healthy Volunteer Study” (Chow, et al., 2010) and “Effect of

Resveratrol on the Pharmacokinetics of Carbamazepine in Healthy Human Volunteers" (Bedada & Nearati, 2015) which measured an increase in carbamezapine levels when coadminstered with RV.

Of the few relevant clinical trials that mention drug interactions, "Resveratrol Does Not Benefit Patients With Nonalcoholic Fatty Liver Disease" (Chachay, et al., 2014) uses 1500mg BID and states "Previous reports have discussed the potential for drug bioavailability interactions as a result of inhibition of the phase I drug metabolism enzyme CYP3A4 by resveratrol. No symptom attributed to drug metabolism was observed, and usual medication prescriptions remained unchanged." Likewise in "Resveratrol as an effective adjuvant therapy in the management of rheumatoid arthritis: a clinical study" (Khojah, Ahmed, Abdel-Rahman, & Elhakeim, 2018) uses 1000mg daily while subjects medications include "leflunomide, hydroxychloroquine, sulfasalazine, methotrexate, prednisolone, and various nonsteroidal anti-inflammatory drugs" states "RSV dose administered without reported adverse events"

As previously mentioned, RV upregulates ACE2 which has previously been shown to reduce inflammation and may be protective against ARDS. However, since ACE2 is also the binding site for SARS-CoV2, a controversial hypothesis was recently published suggesting that the upregulation of ACE2 by blood pressure medication ACE Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs) may increase the risk of infection (Fang, Karakiulakis, & Roth, 2020). This has been countered by a position statement from the European Society of Cardiology (ESC) that states that there is evidence in animal models showing that ACEI and ARBs may be protective in COVID-19 and there are no human evidence showing harm. ESC recommends patients continue ACEI and ARBs (European Society of Cardiology, 2020). There is early evidence is human that ACEI and ARBs may be protective in COVID-19 infection (Sanchis-Gomar F, 2020). On March 17, 2020, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a joint statement advocating for patients to continue ACEIs and ARBs as prescribed and that changes in medications in the setting of COVID-19 should be completed only after careful assessment (American Heart Association, 2020). More recently ACEI and ARBs use has been associated with improved clinical outcomes in COVID-19 patients (Meng, et al., 2020).

2.3.2 KNOWN POTENTIAL RISKS

There are some concerns of adverse effects based primarily on in vitro studies and animal models (Shaito, et al., 2020). While human clinical trials have shown RV to generally be safe and well tolerated at single oral doses of up to 5g, dose related gastrointestinal upset has been reported (Ramírez-Garza, et al., 2018). High doses are associated with inhibition of cytochrome P450 (specifically CYP3A4, CYP2D6, & CYP2C9), which could result in some drug interactions, most concerning for drugs with a narrow therapeutic window. Drug interactions with nicardipine, warfarin, HIV protease inhibitors, anti-arrhythmics, calcium cancel agonists, antihistamines, and immunosuppressants have been reported in animal models (Shaito, et al., 2020). Hydroxychloroquine and chloroquine, drugs that are being investigated for use in COVID-19, are notably metabolized by CYP2C8 and CYP3A4. RV has been reported to enhance the replication of Hepatitis C virus in vitro (Nakamura, et al., 2010).

Noting that RV is associated with upregulation of ACE2 and ACE2 is the binding site for SARS-CoV2, increased ACE2 may facilitate viral entry into the cell (Yan, Xiao, & Lin, 2020).

2.3.3 KNOWN POTENTIAL BENEFITS

- RV may inhibit binding of SARS-CoV2 to the ACE2 receptor which would inhibit viral entry
- RV inhibits TMPRSS2 which could inhibit viral entry into the cell
- RV may inhibit viral protein synthesis, viral RNA synthesis, and viral productions
- RV increases Nitric Oxide (NO), which may independently inhibit viral replication
- RV may be protective from COVID associated stroke by:
    - inhibits Platelet Activating Factor (PAF)
    - inhibiting complement activation
    - vasoprotective effects of nitric oxide
- RV upregulate ACE2 receptor which has been shown to be protective of lung injury
- RV may protect against the effects of the "cytokine storm" storm of COVID-19 by:
    - Inhibiting TLR4
    - Inhibiting NF-κB
    - Inhibiting IL-6
    - Inhibiting TNF-α
    - Inhibiting CCL5 (RANTES)
    - Antioxidant effects

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The main risk of the proposed treatment in prior human studies is GI upset from resveratrol and a theoretical increase risk of infection by coronavirus. GI upset/diarrhea could lead to dehydration and potentially increased risk of renal injury. This is countered by the multiple mechanisms that could prove beneficial in COVID-19.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Reduction in hospitalization rates.	21-day hospitalization or death, defined as admission to any hospital for the treatment of COVID-19, or death, within 21 days of randomization for this study (date of randomization = day 0).	Based on reported typical course of illness for COVID-19 most patients will have declared their need for hospitalization in less than 21 days
Secondary		
Reduction in ICU admission invasive ventilation rates, and ECMO usage rates	ICU admission or death, defined as admission to any intensive care unit (ICU) due to worsening symptoms of COVID-19, or death, among patients who are hospitalized within 21 days of randomization (date of randomization = day 0). Invasive ventilation or death, defined as ventilatory support which requires insertion of an endotracheal tube, or death. ECMO usage or death, defined as the usage of extracorporeal membrane oxygenation machine as an alternative for the management of respiratory failure, or death.	Based on reported typical course of illness for COVID-19 most patients will have declared their need for ICU admission/invasive ventilation/ECMO usage in less than 21 days
Tertiary/Exploratory		
Reduction in morbidity and mortality	Reduction in signs and symptoms based on results of daily surveys. Will also observe mortality rates between groups.	There are mechanisms that would suggest improvements in morbidity and mortality, but this study will likely not have the statistical power to draw firm conclusions.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will be a phase 2, double-blind, placebo-controlled, randomized trial to evaluate the safety and explore the efficacy of resveratrol plus vitamin D3 based on the hypothesis that resveratrol with the adjuncts can reduce hospitalization rates of patient with COVID-19.

Patient Screening and Consent: Potential subjects will present to the Mount Carmel Health System's Emergency Departments, drive through testing stations, or other affiliated ambulatory testing center and undergo testing for SARS-CoV-2 following currently established guidelines and process. Upon confirmation of initial eligibility, research personnel will contact the patient via phone and briefly explaining the study. For patients that express interest in learning more about the study, they will be provided with a website linking to an animated video explaining the study's purpose, risks, and benefits of the trial (see Appendix 12.5 for link to video). If the patient expresses their interest in participating in a COVID-19 trial, they will then have a phone discussion with research personnel to complete verification of all inclusion and no exclusion criteria. If the patient meets any exclusion criteria, they will be thanked for their time and entered into the study screening log. Patients meeting all inclusion and no exclusion criteria will be consented for participation in the trial. The consent process will request access to their health information that is part of any healthcare provider or outpatient visit, or hospitalization that occurs during the 60-day study period. Upon consent, designated personnel will arrange pickup or delivery of the next numbered study agent packet. Participant will be provided written and online video explanation of the study regimen.

Treatment Concealment: Due to reports of patients self-medicating with investigational drugs (e.g., chloroquine) in the setting of COVID-19, we do not intend to reveal the trial substance until after the study is complete. Patients will be informed that they are receiving a "commercially available dietary supplements" which will be described as a "plant extract" that is commonly found in a variety of foods, but the use of RV will not be disclosed. The use of Vitamin D3 will be open-label for both groups. At the end of the study, they will be informed of which study agent they received.

During the enrollment process and after providing consent to participate, subjects will complete a short, online form providing their contact information. Subjects will also be asked to provide the contact information of a spouse, family member or other person in the event the investigator or study personnel lose contact with the subject, so that the subject's status can be determined. The online form is HIPAA-compliant and meets HIPAA regulations for data security. Completion of the form will generate an anonymous study ID associated with that subject and which will be used for other study-related data collection. The study ID does not use any HIPAA-designated identifiers such as birthdate, social security number, etc.

Randomization: The random allocation list will be blocked and stratified by a third-party group or individual. During the trial, only the third-party group and DSMB will have access to the randomization

list, which will be stored on a password-protected computer and/or password-protected file (e.g., REDCap, Excel) by the third-party group or individual. The study personnel will create identical-looking packets with identical-appearing study agents containing a 15-day dosing regimen according to the random allocation list. Study personnel will be blinded to the contents of the distributed packets.

Participant Monitoring and Follow-up: Starting on day 1, and continuing daily for 15 days, subjects will be contacted via e-mail or text message (according to the subject's preference. Messages will include a reminder to take their study medication as scheduled and complete the daily survey (see appendix 12.6.1) each evening prior to going to bed. Subjects will be asked to complete a short questionnaire covering: 1) symptoms they had that day that may be related to COVID-19 (e.g., fever, cough, dyspnea), their frequency and severity; 2) report any other related or non-related medical events; 3) any medications they have taken to relieve symptoms, or other new medications they have not previously reported to study personnel; and 4) any visits they have made to healthcare providers, outpatient centers or hospitals, and details regarding those visits. Subjects will be reminded to contact their primary care physician if they experience symptoms that are worsening or that are concerning to them. For any such contact, they should inform their physician or other healthcare provider that they are enrolled in a clinical trial involving a dietary supplement.

Participants with complete on online PRO-CTCAE questionnaire on days 1, 8 (+1 day), 15 (+1 day), 21 (+1 day), 30, and 60 to monitor for adverse events.

Subjects who do not complete questionnaires will receive a reminder Xe-mails. All patients will be called for a phone interview after 21 days. If subjects cannot be contacted via phone, study personnel will attempt to contact the spouse/family member/friend who is listed as the secondary contact in order to determine the subject's status. A subject will be considered lost to follow-up if their status concerning hospitalization during the study period cannot be verified.

Outcome Assessment and Other Key Variables. Hospitalizations will be determined based on query of subject and/or the subject's secondary contact. The subject's medical records will be requested from the admitting hospital (and discharging hospital, if separate) via a HIPAA authorization.

Additional outcomes will include assessing number of days with fever and to assess symptoms, including dyspnea and fatigue. Questionnaires to assess symptoms will be based on the PRO-CTCAE (see appendix 12.6) (National Cancer Institute, 2020).

Conditions that the CDC defines as being high risk for developing severe COVID-19, and pertinent medications will be recorded. Given the prior safety history of RV and given the potential risks to healthcare workers exposed to COVID-19 patients, we do not intend to obtain laboratory studies as part of this trial.

Assessment for Blinding Integrity and Treatment Adherence. Patients will be asked if they thought they received resveratrol or placebo at 21 (±2) days after enrollment. Patients will be asked report the number of remaining capsules at end of day 16.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

There is no established standard of care for COVID-19 prior to hospitalization. Therefore, this study seeks to establish superiority of the study intervention over a placebo. Due to the previously established safety and tolerability of the study intervention, limited sample size, and time pressure during the COVID-19 pandemic, no dose-response study will be performed at this time.

4.3 JUSTIFICATION FOR DOSE

STUDY AGENT: RESVERATROL

Human clinical trials of RV have used a wide range of dosages (from 10mg to 5g). RV is generally well tolerated with few side effects reported (notable exception being worse outcome in multiple myeloma treatment given a high (single daily 5g) dosage associated with diarrhea/dehydration/renal injury) (Berman, Motechin, Wiesenfeld, & Holz, 2017). An in vitro study of CoV has shown half maximal inhibitory concentration (IC50) of RV as 5.5 µg/ml (Zhang, 2015). While RV is well absorbed, there notably is extensive first pass intestinal and hepatic metabolism of RV. In a study of a single 500mg dose of RV, serum plasma concentration of free-RV reached an average of only 71ng/ml while sulfated-RV reached an average 1516 ng/ml and glucuronated-RV reached 4083 ng/ml (Sergides, Chirilă, Silvestro, Pitta, & Pittas, 2016). The in vitro study showing an IC50 of 5.5 µg/ml (5500 ng/ml) cited above referred to unmetabolized RV. It is unclear to what extent sulfated and glucuronated forms of RV would be metabolically active in vivo against CoV. If only the free form RV is metabolically active against CoV it would be difficult to achieve adequate blood levels to accomplish viral inhibition. Recent molecular modelling of RV derivatives support the concept that glucuronated-RV would be biologically active against SARS-CoV2 by inhibition of papain-like protease and RNA-dependent RNA polymerase. Furthermore, the binding affinity of glucuronated-RV was demonstrated to be superior to the free form of RV (Ranjbar, Jamshidi, & Torabi, 2020). Considering that human trials have shown benefit in even small (10mg) dosing of RV (Berman, Motechin, Wiesenfeld, & Holz, 2017) it would be reasonable to hypothesize that sulfated and/or glucuronated RV are (directly or indirectly, see below) biologically active. In vitro studies have demonstrated that glucuronated RV to be comparably biologically active (Lu, et al., 2013). Tissue concentration of RV is not well understood, but one study of the IV volume of distribution suggested significant extravascular distribution, and a mouse study showed preferential accumulation is tissues (Walle, 2011). Furthermore, it has been suggested that human tissue sulfatases and glucuronidases may locally convert the conjugates back to free-RV (Walle, 2011). The half-life of free-RV is measured at 5 hours, while the half-life of sulfated and glucuronated RV are both about 8 hours (Sergides, Chirilă, Silvestro, Pitta, & Pittas, 2016).

The dosing schedule planned for this study is based on attempting to maximize the plasma levels (and presumably tissue levels) of resveratrol in order to attempt to approach or exceed the minimum inhibitory concentration of the resveratrol against SARS-CoV2. There are not any reported toxic plasma levels associated with orally administered resveratrol. The main limiting factor in the dosing is the concern for GI side effects which is infrequent at doses of 1gm or less (Almeida, et al., 2009) (Boocock, et al., 2007) (Brown, et al., 2010). This goal of viral inhibition is in addition to the anti-inflammatory host benefits.

Prior pharmacokinetic studies have consistently shown low plasma levels of unconjugated RV, with substantially higher levels of sulfated-RV and glucuronidated-RV. The Area Under the Curve (AUC) for glucuronidated-RV is inconsistent in the literature. (Boocock, et al., 2007) (Brown, et al., 2010) (Sergides, Chirilă, Silvestro, Pitta, & Pittas, 2016). There is evidence that the glucuronidated-RV is equally biologically active (Lu, et al., 2013). The is also in vivo evidence that sulfated-RV can serve as a reservoir for unconjugated RV via intracellular sulfatases (Patel, et al., 2013).

Estimates of steady state concentration (C_{ss}) are based on prior pharmacokinetic studies of Area Under the Curve (AUC) divided by the dosing frequency planned for this study (C_{ss}=AUC/ τ) noted below (see Table 1). Prior literature has shown a consistent measurement in the measurement of unconjugated RV, but a wide range of measured resveratrol conjugates. Boocock and Brown measured AUC for 0.5, 1.0, 2.5, and 5gm dosages (Boocock, et al., 2007) (Brown, et al., 2010). Sergides measures AUC based on a single 500mg dose (Sergides, Chirilă, Silvestro, Pitta, & Pittas, 2016). Bioavailability of RV Glucuronide from Sergides, et al notably is a magnitude higher than reported by Boocock or Brown. Based on a 1gm dosage every 6 hours, C_{ss} for unconjugated RV will range from 84 ng/ml (Brown), to 91 ng/ml (Boocock), to 70 ng/ml (extrapolated from Sergides). Considering that the RV conjugates are expected to be biologically relevant it worth noting that the cumulative C_{ss} of RV (including unconjugated, sulfonated, & glucuronidated RV) could range from 2638 ng/ml (Brown) to 2708 ng/ml (Boocock), possibly up to 18,500 ng/ml based on extrapolation on the Sergides data.

Assuming RV conjugates are biologically active against SARS-CoV2, the Sergides data suggests that 4gm daily dosing will exceeded the IC50. The Brown and Boocock data suggest that the oral dosing would not exceed the IC50 of coronavirus.

TABLE 1: AUC & estimated Steady State Serum Concentration

	Total Daily dose in gm	unconjugated RV	4'O glucuronide RV	3'O glucuronide RV	Sulfate RV	**Cumulative RV** Measurements in ng/ml
AUC 1gm (Brown)		503	3774	2087	9464	**15828**
C_{ss} 6hr dosing	4	84	629	348	1577	**2638**
AUC 1gm (Boocock)		544.8	3059	2589	10053	**16245.8**
C_{ss} 6hr dosing	4	91	510	432	1676	**2708**
AUC 0.5gm (Brown)		175	1331	875	3558	**5939**
C_{ss} 6hr dosing	2	29	222	146	593	**990**
AUC 0.5gm (Boocock)		224	1919	1287	4049	**7479**
C_{ss} 6hr dosing	2	37	320	216	675	**990**
AUC 0.5gm (Sergides)		154	33535*		12050	**45739**
C_{ss} 6hr dosing	2	26	5589*		2008	**7623**

*Sergides did not differentiate glucuronidated RV forms

STUDY AGENT: VITAMIN D3

Vitamin D3 (D3) is a fat-soluble vitamin used in this study to enhance the anti-inflammatory effects of RV. While D3 is known for its role in calcium and phosphorus regulation, there is also evidence that it has roles in immunity, inflammation, and cardiovascular health (Maity, Bora, & Sur, 2018). Vitamin D has a role of providing innate immunity including the production of the antimicrobial cathelicidin in respiratory epithelial cells (Hansdottir, et al., 2008). Supplementation of D3 is associated with a decrease in the incidence of viral respiratory infections (Gysin, Dao, Gysin, Lytvyn, & Loeb, 2016). Specific to this study, D3 has been shown to have a synergistic effect with RV and magnifies RV's effect on the inhibition of IL-6 and TNF-α (Maity, Bora, & Sur, 2018) which may play a significant role in the cytokine storm of COVID-19.

D3 deficiency is common worldwide. D3 levels of 30-50ng/ml can modulate inflammatory activities (Zhang, et al., 2012). A single dose of D3 at 100,000 IU (2500mcg) has been shown to reach a mean concentration of 42 ± 9 ng/ml in healthy volunteers. (Ilahi, Armas, & Heaney, 2008) which would be consistent with a level adequate enough to have anti-inflammatory benefits. Vitamin D toxicity is rate

and has been defined by serum levels of >150ng/ml. A daily dose of up to 10,000 IU per day has been described at the upper limit for supplementation in adults (Holick, et al., 2011). Single doses of up with 2,000,000 units (in an accidental overdose) has been well tolerated (Ouweland, Fleuren, Drabbe, & Vollaard, 2014).

Both treatment group and placebo group will receive a single 100,000 IU D3 to differentiate the effects of RV from potential beneficial effects of D3. The use of D3 will be open label for both groups.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study after they have completed a minimum of 7 days of treatment, noting patient will be permitted to discontinue treatment after having 3 days of resolution of fever, fatigure, and dyspnea and they has been followed up with 60 days of enrollment by way of completing the last online survey, exit interview and/or chart review.

The study is considered complete after the last enrolled participant has completed the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

The World Health Organization has categorized baseline severity (see table 1). For this study we will be targeting Mild COVID-19 based on their initial ability to be managed as an outpatient and known estimates for admission rates. Patients who test positive but are asymptomatic (such as being tested for contact tracing) will be excluded from the study as there are no defined estimated for admission rates for asymptomatic patients (patients who become symptomatic can be considered for enrollment).

Furthermore, patients age 45 and greater will be selected for this study due to their higher admission rates. In order to be able to detect a difference in treatment efficacy, a population with a higher admission rate is desirable in order keep the sample size (and its associated cost) down. Noting that, in general, the younger population is more social and may have higher rates of infection, but lower rates of admission including younger age patients in the study would likely skew the population to a low hospitalization rate with resultant difficulty detecting a difference between groups. In addition, in order to avoid unnecessary testing and exposure of healthcare workers to patients with COVID-19, pregnancy will be assessed via self-report of pregnancy potential and report of last menstrual period. The risk of pregnancy will be low in this age group.

Patient must test positive for SARS-CoV2 based on an FDA approved test. Due to low false positive rates and to minimize risk to healthcare providers, minimize the use of PPE and discomfort to the patient, repeat confirmatory testing will not be utilized.

- Outpatients in Central Ohio
- Age ≥45 years
- Mild COVID-19 based on WHO Baseline Severity Categorization (see Table 1)
- Symptom duration ≤ 7 days
- Patient must have access to the internet or a smartphone to complete surveys
- English-speaking patients

Table 1: Baseline Severity Categorization

Disease Severity	Description
SARS-CoV-2 Infection without Symptoms	• Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test • No Symptom
Mild COVID-19	• Positive testing by standard RT-PCR assay or equivalent test • Symptoms of mild illness 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	• Positive testing by standard RT-PCR assay or equivalent test • Symptoms of moderate illness, which could include any symptoms 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 (SaO2) >93% on room air at sea level, heart rate ≥ 90 beats per minute • No clinical signs indicative of Severe or Critical Severity
Severe COVID-19	• Positive testing by standard RT-PCR assay or equivalent test • Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptoms 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 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen (SaO2) <93% on room air at sea level or PaO2/FiO2 <300 mmHg • No criteria for Critical Severity
Critical COVID-19	• Positive testing by standard RT-PCR assay or equivalent test • 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 <90mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors) • Multi-organ dysfunction / failure

Source: WHO R&D Blueprint novel coronavirus

5.2 EXCLUSION CRITERIA

- Diagnosed or suspected cognitive impairment that would prevent the patient from cooperating with study procedures, as judged by the screening clinician.
- Asymptomatic patients (e.g. patients who were screened without symptoms but tested positive).
- Known history of cirrhosis, hepatic impairment, or Hepatitis C
- Known of history of renal impairment as measured by an eGFR of < 60 mL/min.
- Patients receiving chemotherapy or who are on chronic immunosuppressants.
- Allergy to grapes or rice.
- Co-morbidities with a high likelihood of hospitalization within 30 days (e.g., current cancer treatment, severe COPD or CHF)
- Currently pregnant

- Hospitalization
- Co-administration of “statins” and PDE-5 inhibitors must be withheld while on study treatment (see section 6.5).
- Due to concerns of patients taking immunosuppressants and drug interactions in medications with a narrow therapeutic index the use of the the following medications will be exclusionary (Blix, Viktil, Moger, & Reikvam, 2010) (Shaito, et al., 2020).

Immunosuppressants	
Generic Name	**Common Examples**

"Blood Thinners" / NOACs	
warfarin	Coumadin
rivaroxaban	Xarelto
apixaban	Eliquis
dabigatran	Pradaxa

HIV Protease Inhibitors	
atazanavir	Reyataz
darunavir	Prezista
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir/ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir	Invirase
tipranavir	Aptivus
atazanavir/cobicistat	Evotaz
darunavir/cobicistat	Prezcobix

Immunosuppresants	
Janus Kinase Inhibitors	
tofacitinib	Xeljanz
Calcineurin Inhibitors	
cyclosporine	Neoral, Sandimmune, SangCya
tacrolimus	Astagraf XL, Envarsus XR, Prograf
mTOR inhibitors	
sirolimus	Rapamune
everolimus	Afinitor, Zortress
IMDH inhibitors	
azathioprine	Azasan, Imuran
leflunomide	Arava
mycophenolate	CellCept, Myfortic
Biologics	

abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
certolizumab	Cimzia
etanercept	Enbrel
golimumab	Simponi
infliximab	Remicade
ixekizumab	Taltz
natalizumab	Tysabri
rituximab	Rituxan
secukinumab	Cosentyx
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio
Monoclonal Antibodies	
basiliximab	Simulect
daclizumab	Zinbryta
other	
hydroxychloroquine	Plaquenil
chloroquine	Aralen

Seizure medications	
carbamazepine	Tegretol
phenobarbital	Luminol
phenytoin	Dilantin
valproate	Depakote

Cardiac medications	
amiodarone	Cardarone, Pacerone
digoxin	Lanoxin
flecainide	Tambocor
sotalol	Betapace

Psychiatric medications	
lithium	Eskalith

Pulmonary medications	
theophylline	Elixophyllin, Theochron

Antibiotics	
rifampin	Rifadin, Mycobutin

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants will be asked to:

- Discontinue/avoid any dietary supplements not prescribed by their usual healthcare providers
- Women of child-bearing potential will be asked to take a home pregnancy test (provided) prior to the start of the study intervention and report the results via online survey. They will also be also be asked to use some form of contraception during the 15-days they are on the study treatment.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a lack of symptoms at the time they tested positive (e.g. tested positive for contact tracing purposes, but was asymptomatic at the time of screen) may be rescreened if symptoms develop. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

An IRB approved HIPAA waiver will allow for recruitment by contacting patients who test positive for SARS-CoV2 and directly providing information about the trial to the potential participant. All potential participants will be screened for capacity to consent by a study clinician.

Retention will be facilitated by daily reminder emails/surveys and phone calls to participants who do not respond to the online survey.

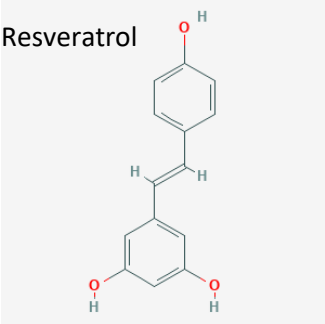
Dose reduction to 1 capsule 4 times per day will be offered to patients considering withdrawing due to GI side effects or who rate their diarrhea as frequently or higher on the PRO-CTCAE 5 point scale.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Chemistry, Manufacturing, and Control:



Study Agent: Resveratrol
Established Name: Trans-Resveratrol
Trade Name: Vita-Age 98% Pure Trans Resveratrol
Manufacturer by Vita-Age, 505-938 Howe Street, Vancouver, B.C. V6Z 1N9, Canada under Good Manufacturing Practices (GMP)
Extracted from Japanese Knotweed Root
Dosage Form: Relabeled bottled containing size 00 capsules of resveratrol from commercially available bottles. Labeling with reflect the route of administration for this study.
Strength: 500mg resveratrol per capsule
Route of Administration: 2 oral capsules 4 times per day
Lot Number for resveratrol raw material: U-F-HZ20200110 (88260-1)
Certificate of Analysis #1 by Vita-Age (see appendix 12.1.2a)
Lot Number for prepared capsules: 20680
Certificate of Analysis #2 for prepared capsules by Labs-Mart Inc, 1938 94 Street NW, Edmonton, AB, Canada (see appendix 12.1.2b)
PubChem CID for resveratrol: 445154 https://pubchem.ncbi.nlm.nih.gov/compound/Resveratrol
Product Label in English (see appendix for full label):

Study Agent: Placebo

Established Name: Placebo

Manufacturer by Vita-Age, 505-938 Howe Street, Vancouver, B.C. V6Z 1N9, Canada under Good Manufacturing Practices (GMP)

Dosage Form: Size 00 capsules containing brown rice flour (sourced from Moore's Flour Mill, 6150 Mill Lane, Redding, CA 96002) to be prepared to be visually indistinct from the treatment capsules. Rice starch is Generally Recognized as Safe (GRAS) NTIS# PB80128804

Route of Administration: 2 oral capsules 4 times per day

Lot Number of brown rice flour: 041620

Certificate of Analysis for Stabilized Brown Rice Flour (see appendix 12.2.1).

Lot Number of prepared capsules: 20677

Certificate of Analysis for prepared Placebo Capsules (see appendix 12.2.2)

Study Agent: Vitamin D3

Established Name: Cholecalciferol

Manufacturer: Ortho Molecular Products, 1991 Duncan Place, Woodstock, IL 60098.

Dosage Form: 50,000 I.U.

Route of Administration: Two capsules once (100,000 IU total), orally on day 1 of the study provided in factor sealed blister pack.

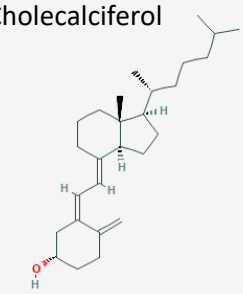
Batch Number: WIP LOT# 83654

Certificate of Analysis: See Appendix 12.3.3

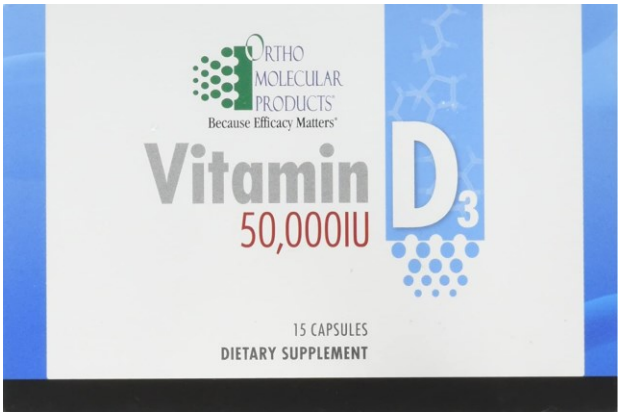
PubChem CID for Cholecalciferol: 5280795

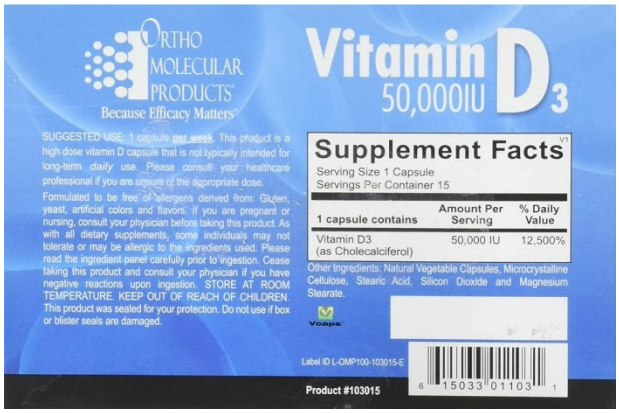
https://pubchem.ncbi.nlm.nih.gov/compound/5280795

Cholecalciferol



Product Label:





6.1.2 DOSING AND ADMINISTRATION

Treatment Group: Two capsules containing resveratrol 500mg each will be taken 4 times per day. A 15-day supply of 120 capsules in manufacturer sealed bottles. Instruction to keep out of reach of children.

Placebo Group:
Placebo group will be administered as two size 00 capsules (that are similar in appearance to the treatment capsules) to be taken 4 times per day. A 15-day supply of 120 capsules in manufacturer sealed bottles. Instruction to keep out of reach of children.

Both Groups:
Both groups will take a single 100,000 IU dose of Vitamin D3 on day 1 of the study, supplied as two 50,000 IU capsules contained in factor sealed blister packs. The use of D3 will be open label for both groups.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator (or designated study personnel) is responsible for ensuring adequate accountability of study drug. This includes acknowledgement of receipt of each shipment of study drug (date, quantity, and condition), and subject dispensing records. Study dispensing records will document the dispensing of the study drug to individual subjects including the date dispensed, subject ID number, and initial of the person dispensing the study drug. Due to concerns of coronavirus contamination, unused study supplies will not be accepted for return and will be disposed of by the participant.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

How Supplied: Participants will receive a manufacturer sealed bottle containing 120 capsules each (15-day supply) of the study agent capsules. Each size 00 capsule will contain either placebo (brown rice flour) or 500mg resveratrol (Vita-Age, Vancouver, BC, Canada).

6.2.3 PRODUCT STORAGE AND STABILITY

Storage at room temperature. Keep out of exposure to sunlight. Stability ≥ 2 years.

6.2.4 PREPARATION

Unmodified commercially available RV capsules and manufacturer prepared placebo capsules contained in manufacturer sealed bottles will be re-labelled with the study instructions. The bottles that have been prepared with study instruction will be turned over to an independent statistical consulting service (professors from Capital University department of Mathematics, Computer Science, and Physics) who will prepare the randomization table. Steps will be put in place to temporarily differentiate placebo vs RV bottles. Tamper-resistant serialized (sequentially numbered) stickers will be assigned to placebo or RV and affixed to the appropriate bottles. Bottles will be returned to the research team differentiated

only by their unique serial number. The randomization table will be kept by OSU's consulting service and forwarded to the DSMB. The research team will only get access to the randomization list only after the completion of the study.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

After receipt of the intervention supplement and placebo, the third-party group will manage the randomization table. Research staff will be blinded to the randomization process.

6.4 STUDY INTERVENTION COMPLIANCE

Participants will document their compliance daily.

Noting that many patients will have a short duration of symptoms (in order to avoid unnecessary side effects), patients will be allowed to discontinue treatment after a minimum of 7 days if they have been symptom free for 3 days. Completion of a minimum of 7 days of treatment whose symptoms have resolved will be consider compliant with treatment.

In case of a single missed dosage, patient will be asked to divide the 2 missed capsules amongst their next 2 dosages. Patient is not to take more than 3 capsules at a time, and no more than 9 capsules in a day.

At the end of the study, participants will report the number of remaining capsules in their bottles at the end of 15 days.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

Patients will be asked to discontinue any over-the-counter supplements/vitamins not prescribed by their physicians. Participants taking vitamin D prescribed by their physician will be asked to discontinue vitamin D for 1 month.

Patients on "statin" cholesterol lowering medication (e.g. simvastatin, lovastatin, etc.) and PDE-5 inhibitors (Viagra, Cialis, etc.) who would like to enroll in this study will be asked to discontinue these medications while on the study medication due to concerns for drug interactions. (Detampel, Beck, Krähenbühl, & Huwyler, 2012).

Patients on NSAIDs will be cautioned about increase risk of GI side effects and to avoid maximum dose NSAIDS. Patients on chronic high dose NSAIDS will be excluded from the study.

Noting that resveratrol is associated with increased insulin sensitivity, diabetics will be cautioned that the supplement could increase their risk of hypoglycemia and that they should monitor their blood glucose closely. (Poulsen, et al., 2013)

See also the exclusion criteria (section 5.2) for list of contraindicated medications.

Non-Trial Investigational Agents: During their participation in the study, subjects will be instructed against participating in other interventional clinical trials, or otherwise avoid taking non-trial investigational agents, unless they are hospitalized and/or their physician judges that participation in another clinical trial is necessary for obtaining the best health outcome after infection with SARS-CoV-2. If patient is prescribed hydroxychloroquine or chloroquine, they will be instructed to discontinue RV.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The study agent will be discontinued if the patient is admitted to the hospital.

The data to be collected at the time of study intervention discontinuation will include the following:

- Interview that participant regard their concern for discontinuation and assess for side effects/safety concerns.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Subject withdraws consent
- Subject voluntarily withdraws from treatment
- Subject is unable to tolerate continued study drug administration
- Significant study intervention non-compliance
- Subject experiences a Grade 3 or higher adverse event attributed to the study drug by the investigator
- Subject experiences a Grade 3 or higher clinically significant laboratory abnormality attributed to the study drug by the investigator
- Subject's clinical condition has worsened to be considered "severe" or "critical"
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Subject becomes pregnant
- Subject becomes lost to follow-up

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

Patients that discontinue/withdraw from the study will continue to be followed for a minimum of 21 days after randomization to assess outcomes/hospitalization rates as allowed.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if we are unable to determine the patient's outcome

via participant survey, email correspondence, phone call to participant, phone call to secondary contact, and if information regarding their condition cannot be determined via the electronic medical record including after attempting to obtain records from surrounding hospital systems (Ohio State University and OhioHealth). Vital record search will also be used, if necessary, to determine outcomes in participants lost to follow up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Outcome Assessment and Other Key Variables. Hospitalizations will be determined based on query of subject and/or the subject's secondary contact. The subject's medical records will be requested from the admitting hospital (and discharging hospital, if separate) via a HIPAA authorization.

Additional outcomes will include daily reporting of fever to assess number of days with fever and assess severity of dyspnea and fatigue. Questionnaires to assess symptoms and adverse events will be used to monitor patients based on the PRO-CTCAE (see appendix 12.6) (National Cancer Institute, 2020).

Conditions that the CDC defines as being high risk for developing severe COVID-19, and pertinent medications will be recorded.

Adverse events will be recorded using PRO-CTCAE and CTCAE.

8.2 SAFETY AND OTHER ASSESSMENTS

Safety Monitoring. This study while only be initiated after approval by Mt Carmel Health System's Research Advisory Review Committee (RARC), Institutional Review Board (IRB), and the Food and Drug Administration (FDA).

An independent Data and Safety Monitoring Board (DSMB) will been convened to assess the progress of a clinical study, the safety data, and critical efficacy endpoints (if appropriate) and provide recommendations. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and data integrity of the study. The charter for the DSMB was developed by the Trinity Health research department.

In addition to daily self-assessment via survey, participants will be provided with a consumer grade finger pulse oximeter. They will be instructed to (at minimum) record their resting pulse oximeter reading of pulse rate and oxygen saturation each evening. Patients will be instructed to seek medical attention for best resting oxygen saturation (SaO2) <94% on room air, or resting heart rate ≥ 90 beats per minute. Patients will be cautioned faulty readings and techniques for accurate readings. Consumer grade pulse oximeters report an accuracy of +/- 2%.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

For this study, an adverse event is defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." [21 CFR 312.32(a)] At the dosing used in this study, the investigators do not anticipate a higher than minimal risk of adverse events which occur

due to the use of resveratrol. Data on adverse events will be collected for this study via the online questionnaires based on as selection of PRO-CTCAE questions as well as exit interviews graded according to the Common Terminology Criteria for Adverse Events (CTCAE) and assessed for their potential relationship to the study agent (see: https://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Data safety monitoring will be conducted by an independent Data Safety Monitoring Board. The DSMB biostatistician will prepare reports for the principal investigator which summarizes the adverse events and serious adverse events, by group (labelled 'A' and 'B'), type of event and frequency. An initial planned interim safety analysis of the first 100 participants by the DSMB will occur after the first 21-day data is collected from the 100th participant. Enrollment of new subjects will be paused pending the results of DSMB review the first 100 participants. The study will resume enrollment upon DSMB approval. The monitoring Institutional Review Board (IRB) will receive all serious adverse event reports generated for this trial. Decisions regarding stopping the trial for safety reasons will be made after consultation with the IRB and/or DSMB.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event is an adverse event that, in the opinion of the investigator or sponsor, results in: 1) death or is life-threatening (immediate risk of death); 2) hospitalization or prolongation of existing hospitalization; 3) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability); or 4) congenital anomaly / birth defect.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 Severity of Event

In general, grade categories are described as follows:
– **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
– **Grade 2** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life
– **Grade 3** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
– **Grade 4** Life-threatening consequences; urgent intervention indicated.
– **Grade 5** Death related to AE.

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 Expectedness

Research physicians will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention

Expected RV AE		
Diarrhea	Nausea	Gas/Bloating
Expected COVID AE		
Fever	Fatigue	Dry Cough
Loss of appetite	Body Aches	Shortness of breath
Mucus/phlegm	Sore Throat	Headache
Chills	Loss of smell/taste	Stuffy nose
Nausea or Vomiting	Diarrhea	Stroke
Conjunctivitis	Lower extremity numbness, swelling, pain	"COVID Toes"
Arrhythmias	Heart Attacks	Cardiomyopathy
Pulmonary Embolism	Death	

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel by way of participant online survey results and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Research clinicians will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events (AEs) will be recorded in the Case Report Form (CRF), and will be reviewed on an ongoing basis by the investigator and DSMB. The Principal Investigator shall be solely responsible for complying, within the required timelines, with any safety reporting obligation to competent Health Authorities and the IRB, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis).

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Any SAE identified by research personnel must be reported to the Principal Investigator with notification copied to the DSMB as soon as practicable, but within 24 hours.

- Initial reporting: IND application principal investigator/sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

  Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

- Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.
- All IND safety reports must be submitted on Form 3500A https://www.fda.gov/media/69876/download

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be contacted as soon as practicable, via email, phone, or letter about any adverse events defined at "potentially related," "probably related," or "definitely related" to the study that are specifically related to the individual participant. A record of the communication will be recorded in the REDCap data collection system.

Upon completion of the study, participant will be emailed a summary of the study results written in layman terminology describing aggregate results of the study including a summary of adverse events and unanticipated problems believed to be related to the study.

8.3.8 EVENTS OF SPECIAL INTEREST

Any identified events not covered above, such as discovery of abnormal lab test results, study intervention overdose, or events that raise concern by the research clinician will be reported to the principal investigator and/or DSMB.

8.3.9 REPORTING OF PREGNANCY

If patient reports pregnancy during the study, they will be asked to discontinue the study intervention. Consent to follow the pregnancy outcome will be requested.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or probably related to participation in the research ("probably related" means there is a reasonable probability that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and DSMB as soon as practicable but within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and DSMB within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.
- https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be contacted as soon as practicable, via email, phone, or letter about any adverse events defined by study that are specifically related to the participant. A record of the communication will be recorded in the REDCap data collection system.

Upon completion of the study, participant will be emailed a summary of the study results written in layman terminology describing aggregate results of the study including a summary of adverse events and unanticipated problems believed to be related to the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Hospitalization (less frequent is better)

Null hypothesis: There is no difference between resveratrol and placebo with respect to the proportion of patients hospitalized or deceased within 21 days of randomization.

Alternative hypothesis: There is a difference between resveratrol and placebo with respect to the proportion of patients hospitalized or deceased within 21 days of randomization.

- Secondary Efficacy Endpoint(s):

ICU admission (less frequent is better)
Null hypothesis: There is no difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients admitted to the ICU or deceased.
Alternative hypothesis: There is a difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients admitted to the ICU or deceased.

Invasive ventilation (less frequent is better)
Null hypothesis: There is no difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients receiving invasive ventilation or deceased.
Alternative hypothesis: There is a difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients receiving invasive ventilation or deceased.

Extracorporeal membrane oxygenation (ECMO) (less frequent is better)
Null hypothesis: There is no difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients receiving ECMO or deceased.
Alternative hypothesis: There is a difference between resveratrol and placebo among patients who are hospitalized within 21 days of randomization with respect to the proportion of patients receiving ECMO or deceased.

9.2 SAMPLE SIZE DETERMINATION

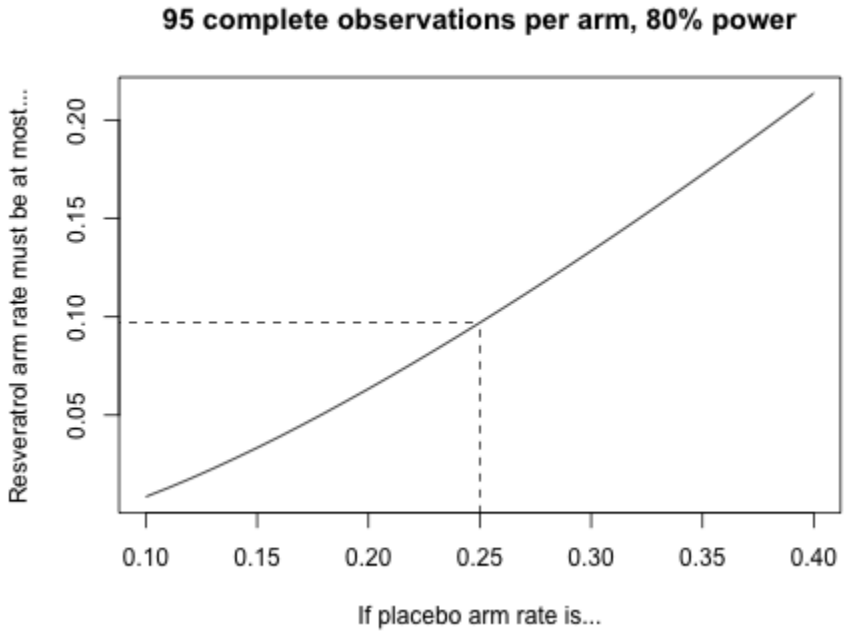
The maximum total number of randomized subjects is capped at 200 by FDA request. We present power analyses of the primary outcome measure (hospitalization) assuming multiple placebo arm

hospitalization rates and effect sizes, as well as for secondary outcome measures. No interim analyses for efficacy are planned, and none are included in the following power calculations.

The primary outcome measure is hospitalization within 21 days of randomization. We provide conservative power estimates by assuming a binary outcome with 5% non-informative loss to follow-up before 21 days. We anticipate this relatively low rate of loss because the endpoint is designed to be evaluable by chart review unless the subject withdraws consent. Hypotheses are as specified in the previous section, and the Z statistic for a two-proportion test is used. The primary Kaplan-Meier analysis will yield slightly better power by treating the outcomes of patients lost to follow-up as censored at the time of last follow-up.

The rate of hospitalization among confirmed cases of COVID-19 ranges between 21% in the 45-54 age bracket, up to 31% for patient's >85 (CDC, 2020). We assumed a mid-point hospitalization rate of 25% for the initial sample size calculation. To achieve 80% power at the 5% two-sided significance level with complete follow-up on 95 subjects per arm with two-sample proportion test, we require a 10% or lower hospitalization rate in the resveratrol arm, compared to a 25% rate in the placebo arm (estimated by `power.prop.test`, R statistical software). This corresponds to an odds ratio of 1 / 3.

The required resveratrol arm event rate for various placebo arm event rates are plotted in Figure 3. This curve applies to the power for all outcome measures, with lower rates of all secondary outcome events expected to be lower in both arms.



9.3 POPULATIONS FOR ANALYSES

- Intention-to-treat (ITT) population: all randomized participants.
- Safety population: all randomized participants who report taking at least one dose of their assigned medication.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Uncensored data will be summarized by percentages, means and standard deviations, or medians and ranges as appropriate for each variable's distribution. Data subject to censoring (e.g., hospitalization) will be summarized by Kaplan-Meier estimate.

Unless otherwise noted, all hypothesis tests will be two-sided and at the 5% significance level. Similarly, confidence intervals will be two-sided and at the 95% confidence level. Declarations of superiority will be declared if the corresponding hypothesis test is significant and the direction of the estimated treatment effect is favorable to resveratrol.

In addition to local hypothesis tests, we will use a multiple testing procedure to control the familywise Type I error at 5% for the primary and secondary endpoints together. The primary efficacy endpoint (hospitalization) will be tested at the 5% significance level; then, if the primary endpoint null hypothesis is rejected, the two secondary endpoints (ICU admission, invasive ventilation) will be tested via the Bonferroni-Holm procedure. No multiple testing adjustment will be made for exploratory or safety analyses.

Hospitalization, ICU admission, and invasive ventilation endpoints are composites that include death within 21 days of randomization.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is hospitalization for any cause within 21 days after randomization, as established by medical record review. Outcomes of subjects who withdraw consent or are otherwise lost to follow-up before 21 days will be considered missing. The intention to treat population for the hospitalization endpoint will be used for analysis. A logistic regression model will be fit with age, sex, race, ethnicity, risk group (see Sec 9.4.7), and randomized group as covariates, with the coefficient to randomized group as the primary estimand. Missing outcome data will be imputed using multiple imputation based on predictions from the logistic regression model of the outcome. Sensitivity analyses will include analyses in which patients lost to follow-up are assumed to not have been hospitalized, and tipping-point analyses systematically and comprehensively varying assumptions about missing outcomes on the treatment and placebo arms independently.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints are ICU admission or death and invasive ventilation or death within 21 days after randomization, as established by medical record review. Outcomes of subjects who withdraw

consent or are otherwise lost to follow-up before 21 days will be considered missing. The intention to treat population for each endpoint will be used for analysis. Estimation and testing procedures will follow those of the primary efficacy endpoint.

9.4.4 SAFETY ANALYSES

Adverse events will be coded according to the Common Terminology Criteria for Adverse Events (CTCAE), and each AE will be counted at most once per participant. Severity, frequency, and relationship of AEs to the study intervention will be presented by System Organ Class and preferred term groupings. Start date, stop date, severity, relationship, expectedness, outcome, and duration will be reported for each AE. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be tabulated. The safety population will be used for safety analyses.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics, including demographics and baseline risk factors. Sample proportions, means and standard errors, or medians and ranges will be provided as appropriate for each distribution. No inferential statistics will be used. Descriptive statistics will be reported for the intention-to-treat population.

9.4.6 PLANNED INTERIM ANALYSES

An independent DSMB will monitor safety data on a continual basis throughout the trial. One interim analysis will be carried out after the first 100 patients have completed the initial 21-day study period. After 100 patients have been randomized, enrollment will pause until all randomized patients have completed at least 21 days of follow-up to evaluate the primary endpoint and the interim analysis has been completed. The DSMB can recommend enrollment suspension or study termination for reasons of safety. Study enrollment will be suspended by the PI when (1) any subject experiences a Grade 3 or higher adverse event toxicity (defined in 8.3.3.1) that is probably, or definitely related to the study agent, or when (2) stopping is indicated by the statistical stopping rule defined below. An enrollment suspension under either scenario will trigger an ad hoc safety review by the DSMB. Following DSMB review and recommendation, the IRB and FDA will determine whether study enrollment will resume.

The interim and final analyses will use the Hwang-Shih-DeCani alpha spending function with parameter gamma = -4 (O'Brien-Fleming–like) for the upper (superiority) bound under the null hypothesis with total one-sided Type I error 2.5%, and for the lower (safety or futility) bound under the alternative hypothesis with total Type II error 20% (80% power). Under the assumption of a binding futility bound and a placebo arm hospitalization rate of 25%, the probability of declaring futility at the interim analysis is 3% if the resveratrol arm hospitalization rate is 10% (alternative hypothesis), 55% if the resveratrol arm hospitalization rate is 25% (null hypothesis), and 75% if the resveratrol arm hospitalization rate is 30%. The R package `gsDesign` will be used to determine stopping boundaries.

9.4.7 SUB-GROUP ANALYSES

Stratified versions of the primary and secondary efficacy endpoint analyses will constitute exploratory subgroup analyses, with each variable analyzed separately. Variables defining strata are as follows.

- Age (65 or older versus 64 or younger)
- Sex
- Race
- Ethnicity
- Presence of at least one factor indicating membership in a high-risk group:
    - Blood disorder, including sickle cell disease or taking blood thinners.
    - Chronic kidney disease.
    - Chronic liver disease.
    - Compromised immune system (e.g., on chemotherapy, high dose steroids, immunosuppressant medications, HIV/AIDS).
    - Heart disease.
    - Lung disease.
    - Neurologic disease.
- ACE inhibitor / ACE Receptor Blocker (ARB) use.

Age is included due to known association with risk of complications due to COVID-19. Sex, race, and ethnicity are included in compliance with the NIH policy on the Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Comorbidity and concomitant medication risk factors are combined to limit the multiplicity of comparisons.

A formal multiplicity-corrected subgroup analysis procedure will be carried out via credible subgroups (Schnell, 2016). A logistic regression model will be fit with age and presence of at least one factor indicating membership in a high-risk group, their interactions with study arm, and study arm alone. Bounds for the benefiting subpopulation of patients, defined by age (as a continuous variable) and risk category will be computed at the 80% credible level.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be presented.

9.4.9 EXPLORATORY ANALYSES

Three classes of exploratory analyses will be executed in the modified intention-to-treat populations for the respective outcome measures:

1. Analyses of morbidity and mortality
2. Log-rank tests for non-covariate-adjusted differences in survival curves through 21 days post-randomization
3. Covariate-adjusted analyses

Morbidity and mortality will be analyzed following the procedure for the primary efficacy endpoint, in the modified intention-to-treat population for each endpoint.

Of primary interest for efficacy endpoints is the event rate at 21 days post-randomization. However, we will also report log-rank tests comparing survival curves between randomized arms throughout the follow-up period.

Cox proportional hazards fits will be reported, including effect estimates, standard errors, and tests for study arm, age, sex, race, and presence of at least one factor indicating membership in a high-risk group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

- Institutional Review Board (IRB)-Approved Consent form
- Slides summarizing animated presentation of the study

10.1.1.2 Consent Procedures and Documentation

- Partial Waiver of Authorization for recruitment purposes obtain from the IRB. Patients will be recruited from electronic reports of potential participants.
- Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The consent process will be completed online. The patient will be provided with an animated presentation (approximately 3-5 minutes in length) explaining the study and its risks, and benefits. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The participant will be given the opportunity to ask the investigator any questions that may arise. The participant will be provided with a link to the Office of Human Resources Protection "About Research Participation" webpage as an addition resource. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will electronically sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented, and the form signed, before the participant undergoes any study-specific treatment. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to, study participants, investigator, or/and regulatory

authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored electronically, in a HIPAA Compliant, password secured database, for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will stored in the REDCap (Harris, et al., 2009) data collection platform. Access to protected health information will be restricted to the research clinician. Individual participants and their research data will be identified by an anonymized unique study identification number for statistical analysis and scientific reporting. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at an encrypted, firewall and password protected research data repository

managed by Mount Carmel Health System Information Security (IS) and the Mount Carmel Health System Office of Research Affairs (ORA).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in the REDCap Data Collection software platform on a HIPAA compliant server maintained by Trinity Health Systems (the parent company of Mt Carmel Health Systems. After the study is completed, the de-identified, archived data will be transmitted to and stored in the REDCap system.

There will be no biological specimens collected as a part of this trial.

When the study is completed, access to study data and/or samples will be provided through research data repository managed by Mount Carmel Health System Information Security (IS) and the Mount Carmel Health System Office of Research Affairs (ORA).

10.1.5 Key Roles and Study Governance

Principal Investigator	**Safety Monitor**	**DSMB - Members**
Marvin McCreary, MD	Ashley Patel, MD	Lynn Shaffer, PhD (Chair)
Mt Carmel Health Systems	Mt Carmel Health Systems	Brian Hamburg, MD
		Sean Lansing, PhD

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including Lynn Shaffer, PhD (statistics, epidemiology), Brian Hamburg, MD (pulmonologist), and Sean Lansing (ethics). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will receive data to assess safety and efficacy data on each arm of the study after each quartile of participants have completed the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to Principal Investigator

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International

Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The principal investigator or designee will at least weekly review the results of the patient survey data assess patient's progress and condition.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Principal investigator and/or safety monitor will verify that the clinical trial is conducted and data are generated , documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 Data Collection and Management Responsibilities

Data will be collected electronically via the REDCap (Research Electronic Data Capture) platform (Harris, et al., 2009).

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

A copy of the patient's consent form will be provided to the Mt Carmel Health Systems Medical Record Department to be recording in the patient's Electronic Medical Record.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the Trinity Health. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 3 years after the completion of the study, a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in a peer reviewed journal.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts disclosed and managed in a way that is appropriate to

their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CoV	Coronavirus
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D3	Vitamin D3
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PPE	Personal Protective Equipment

PRO-CTCAE	Patient Reported Outcome - CTCAE
QA	Quality Assurance
QC	Quality Control
RV	Resveratrol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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12 APPENDIX

12.1 RESVERATROL

12.1.1 PRODUCT LABEL

12.1.2A CERTIFICATE OF ANALYSIS FOR RESVERATROL RAW MATERIAL

VITA-AGE®
505-938 Howe Street, Vancouver. B.C. V6Z 1N9 Canada
Toll-Free: 1-888-984-4498 Tel: 1-604-331-4488
Email Address : info@vitaage.com
Health Canada Santé Canada SL#301991

CERTIFICATE OF ANALYSIS

Product Name	Polygonum cuspidatum extract	**Batch Number**	U-F-HZ20200110
Botanical Latin Name	Polygonum cuspidatum Sieb. et Zucc.	**MFG. Date**	Jan. 10, 2020
Plant Part	Root	**Retest Date**	Jan. 9, 2022
Batch Size	600kg	**Solubility**	Good solubility in alcohol

ITEM	SPECIFICATION	RESULT	TEST METHOD
Physical Description			
Appearance	White powder	Conforms	Visual
Odor	Characteristic	Conforms	Organoleptic
Taste	Characteristic	Conforms	Olfactory
Particle size	100% pass through 80 mesh sieve	Conforms	CP2015
Chemical Tests			
Resveratrol	98% Min	Conforms	HPLC
Loss on drying	≤1%	Conforms	CP2015
Ash	≤0.50 %	Conforms	CP2015
Heavy Metals	≤10 ppm	Conforms	CP2015
Lead (Pb)	≤3 ppm	Conforms	CP2015
Arsenic (As)	≤2 ppm	Conforms	CP2015
Cadmium (Cd)	≤1 ppm	Conforms	CP2015
Mercury (Hg)	≤0.5 ppm	Conforms	CP2015
Microbiology Control			
Aerobic bacterial count	≤1,000 cfu/g	Conforms	CP2015
Total Yeast & Mold	≤100 cfu/g	Conforms	CP2015
Escherichia coli	Negative	Conforms	CP2015
Salmonella	Negative	Conforms	CP2015

12.1.2B THIRD PARTY CERTIFICATE OF ANALYSIS FOR RESVERATROL RAW MATERIAL

Labs-Mart Inc.
1938 94 Street NW
Edmonton, AB, Canada, T6N 1J3
T 780-469-9009 F 780-469-9080

LABS•MART Inc.
Analytical Services and Consultation

REPORT # 88260-1

To Vita-Age Nutrition
505-938 Howe Street
Vancouver, BC, V6Z 1N9
T 604-331-4488

Date 2020-04-06

Received 2020-03-31

TRANS-RESVERATROL 98%; Lot# U-F-HZ20200110 (88260-1)

Test	Specification	Test Result	Method	Analyst	Date	Loc.
Resveratrol	98%	98.0%	HPLC-UV	XL	2020-04-03	BC

Labs-Mart Testing Locations:

BC - 240 - 3751 Jacombs Road, Richmond, BC, Canada

Prepared by _____ Approved by _____ Date 2020-04-06
Christine Albrecht, Account Manager Mohammad Rafik Shaikh, QC Speciali

Page 1 of 1

12.1.3 Certificate of Analysis for Prepared Capsules

Labs-Mart Inc.
1938 94 Street NW
Edmonton, AB, Canada, T6N 1J3
T 780-469-9009 F 780-469-9080

LABS-MART Inc.
Analytical Services and Consultation

REPORT # 90171-2
Date 6/24/2020
Received 2020/06/16

To Vita-Age Nutrition
505-938 Howe Street
Vancouver, BC, V6Z 1N9
T 604-331-4488

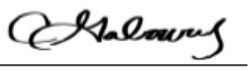
VITA-AGE RESVERATROL; Lot# 20680 (90171-2)

Test	Specification	Test Result	Method	Analyst	Date	Loc.
Arsenic	N/A	<0.03 ppm	ICP-MS	JH	2020/06/23	AB
Cadmium	N/A	<0.02 ppm	ICP-MS	JH	2020/06/23	AB
Lead	N/A	2.02 ppm	ICP-MS	JH	2020/06/23	AB
Mercury	N/A	<0.02 ppm	ICP-MS	JH	2020/06/23	AB
1. Total Plate Count	N/A	<10 CFU/g	USP <2021/2022>	OM	2020/06/22	AB
2. Yeast & Mold	N/A	<10 CFU/g (Yeast); 600 CFU/g (Mold)	USP <2021/2022>	OM	2020/06/22	AB
3. S. aureus	N/A	Negative	USP <2021/2022>	OM	2020/06/22	AB
4. E. coli	N/A	Negative	USP <2021/2022>	OM	2020/06/22	AB
5. Salmonella	N/A	Negative	USP <2021/2022>	OM	2020/06/22	AB
Resveratrol	500 mg/capsule	460 mg/ 514.17 mg	HPLC-UV	SMC	2020/06/23	AB

*Based on a unit weight of 514.17 mg

Labs-Mart Testing Locations:

AB - 1938 94 Street, Edmonton, AB, Canada

Prepared by  Chantelle Gaboury, Account Manager

Approved by  Mohammadrafik Shaikh, QC Specialist

Date 2020/06/24

12.1.3 STABILITY REPORT

VITA-AGE®
505-938 Howe Street, Vancouver. B.C. V6Z 1N9 Canada
Toll-Free: 1-888-984-4498 Tel: 1-604-331-4488
Email Address : info@vitaage.com
Health Canada Santé Canada
SL#301991

Stability Test Report

Product Name	Giant Knotweed Extract, Resveratrol 98%		
Batch Number	U-F-BLLC20180320		
Test date	20180320		

Item of Analysis	**Sanitary standard value**	**Testing Result**				
		0 Month	**6 Month**	**12 Month**	**18 Month**	**24Month**
Assay Resveratrol	98%	98.21%	98.19%	98.15%	98.11%	98.08%
Appearance	Off-white	Conforms	Conforms	Conforms	Conforms	Conforms
Odor	Characteristic	Conforms	Conforms	Conforms	Conforms	Conforms
Taste	Characteristic	Conforms	Conforms	Conforms	Conforms	Conforms
Loss on drying	5%NMT (%)	3.49%	3.52%	3.55%	3.59%	3.62%
Total ash	5%NMT (%)	2.57%	2.59%	2.62%	2.66%	2.69%
Lead (Pb)	2ppm NMT	Conform	0.7ppm	0.7ppm	0.7ppm	0.7ppm
Arsenic (As)	2ppm NMT	Conform	0.36ppm	0.36ppm	0.36ppm	0.36ppm
Cadmium (Cd)	1ppm NMT	Conform	0.28ppm	0.28ppm	0.28ppm	0.28ppm
Mercury (Hg)	0.1ppm NMT	Conform	0.019ppm	0.019ppm	0.019ppm	0.019ppm
Total Plate Count	1000cfu/g Max	Conform	Less Than500	Less Than500	Less Than500	LessThan500
Yeast & Mold	100cfu/g Max	Conform	Less Than10	Less Than10	Less Than10	Less Than10
E. Coli.	Negative	Conform	Negative	Negative	Negative	Negative
Salmonella	Negative	Conform	Negative	Negative	Negative	Negative
Staphylococcus	Negative	Conform	Negative	Negative	Negative	Negative
Conclusion	Conform					

505-938 Howe Street, Vancouver, BC, V6Z 1N9 - Tel: (604)331-4488 - Fax: (604)331-4428
Website: www.vitaage.com E-mail: info@vitaage.com

12.1.4 GMP CERTIFICATE

chfa

CERTIFICATE OF GMP COMPLIANCE	CERTIFICATE NO.: *CERTIFICAT Nº :* 553436	CERTIFICAT DE CONFORMITÉ AUX BPF

This Certificate of Good Manufacturing Practice (GMP) Compliance is issued by the Canadian Health Food Association/ Association canadienne des aliments de santé délivre le présent certificat.

SITE LICENCE HOLDER INFORMATION / *RENSEIGNEMENTS SUR LE TITULAIRE DE LICENCE D'EXPLOITATION*

NAME OF APPLICANT: *NOM DU DEMANDEUR :*	RAFA RIVER NATURALS CANADA INC.		
STREET ADDRESS: *ADRESSE :*	13520 CRESTWOOD PLACE, UNITS 14 & 15		
CITY: *VILLE :*	RICHMOND	PROVINCE: *PROVINCE :*	BRITISH COLUMBIA
COUNTRY: *PAYS :*	CANADA	POSTAL CODE: *CODE POSTAL :*	V6V 2G3

SITE INFORMATION / *RENSEIGNEMENTS SUR LE SITE*

AUTHORIZED ACTIVITIES / *ACTIVITES AUTORISEES*	SITE ADDRESS / *ADRESSE DU SITE*	SITE LICENCE NO / *NO. DE LICENCE D'EXPLOITATION*	DATE OF EXPIRY / *DATE D'EXPIRATION*
MANUFACTURING / *FABRICATION:*	13520 CRESTWOOD PLACE, UNITS 14 & 15, RICHMOND BC V6V 2G3	301472	AUGUST 24, 2020
PACKAGING / *EMBALLAGE:*	13520 CRESTWOOD PLACE, UNITS 14 & 15, RICHMOND BC V6V 2G3	301472	AUGUST 24, 2020
LABELLING / *ÉTIQUETAGE:*	13520 CRESTWOOD PLACE, UNITS 14 & 15, RICHMOND BC V6V 2G3	301472	AUGUST 24, 2020
IMPORTING / *IMPORTATION:*			

CERTIFYING AUTHORITY INFORMATION / *RENSEIGNEMENTS SUR AUTORITÉ DE CERTIFICATION*

ADDRESS OF CERTIFYING AUTHORITY:

CANADIAN HEALTH FOOD ASSOCIATION
235 YORKLAND BLVD, SUITE 201
TORONTO, ONTARIO M2J 4Y8

ADRESSE D'AUTORITÉ DE CERTIFICATION:

ASSOCIATION CANADIENNE DES ALIMENTS DE SANTE
235, YORKLAND BLVD, BUR 201
TORONTO (ONTARIO) M2J 4Y8

NAME OF CHFA AUTHORIZED OFFICIAL /
NOM DU RESPONSABLE AUTORISÉ DE LA CHFA:

Canada 2018 5004427 chfa Canadian Health Food Association

INTERNATIONAL TRADE CERTIFICATE ISSUANCE OFFICER,
CANADIAN HEALTH FOOD ASSOCIATION

DATE OF ISSUANCE:
DATE DE DÉLIVRANCE : OCT 0 3 2018

Page 1 of 1

12.2 PLACEBO

12.2.1 CERTIFICATE OF ANALYSIS FOR BROWN RICE FLOUR

VITA-AGE®
505-938 Howe Street, Vancouver. B.C. V6Z 1N9 Canada
Toll-Free: 1-888-984-4498 Tel: 1-604-331-4488
Email Address : info@vitaage.com
Health Canada Santé Canada
SL#301991

Certificate of Analysis

Moores' Flour Mill
6150 Mill Lane
Redding, CA 96002
530-241-9245

Product Description: Stabilized Brown Rice Flour **Lot Number:** 041620

SIEVE ANALYSIS

	RESULT
On U.S. #40	0.00%
On U.S. #50	38.00%
On U.S. #80	8.00%
Thru U.S. #80	54.00%

MOISTURE ANALYSIS

RESULT
11.93%

RECEIVED MAY 13 2020 34.08 kg

12.2.2 CERTIFICATE OF ANALYSIS FOR PREPARED CAPSULES

RAFA RIVER NATURALS CANADA INC.
14-13520 Crestwood Place, Richmond, B.C. V6V 2G3
Tel: 604-233-1117 Fax: 1-888-775-2821
Email: info@rafariver.com

CERTIFICATE OF ANALYSIS

Report Date:	June 10, 2020
Product Name:	Placebo Vegetarian Capsules
Lot No:	**20677**
Customer:	Canton Global Trading

Description	A clear, #00 vegetarian capsule Filled with fine, dense powder, free from impurities		
Colour	Capsule: body-natural cap- natural Powder: Beige		
Odour	Characteristic		
Ingredients	Each capsule contains:		
	Brown Rice Flour		850 mg
	Magnesium Stearate		5 mg

Tests	**Test Method**	**Limits**	**Results**
Filling Weight Variation	USP <905>	855 mg ± 5%	Conform
Gross Weight Variation		980 mg ± 5%	Conform
Disintegration	USP <701>	< 45 min.	Conform
Heavy Metal Testing	**<maximum daily dose: 5.880 g>**		
Arsenic	ICP/MS	< 0.14 µg/kg b.w/day	< 0.0109 µg/kg
Cadmium	ICP/MS	< 0.09 µg/kg b.w/day	< 0.0008 µg/kg
Lead	ICP/MS	< 0.14 µg/kg b.w/day	< 0.0008 µg/kg
Mercury	ICP/MS	< 0.29 µg/kg b.w/day	< 0.0008 µg/kg
Microbiological Testing	**USP <2021>,<2022>**		
Standard Plate Count		<100,000 cfu/g	Conform
Escherichia coli		Negative	Negative
Salmonella		Negative	Negative
Staphylococcus aureus		Negative	Negative
Yeast and Mold		<10,000 cfu/g	Conform

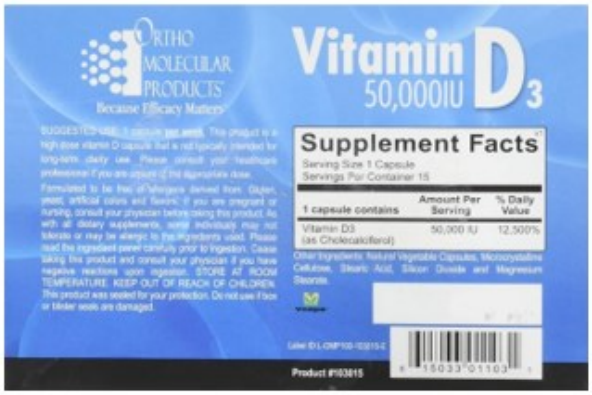
Packaging	120 capsules / 225cc bottle
Expiry Date	01/2022 **(Not Labeled)**
Storage	Sealed, Store in a cool, dry place Keep out of reach of children

Quality Assurance/Quality Control

6/10/2020
Date

12.3 VITAMIN D3 (CHOLECALCIFEROL)

12.3.1 PRODUCT LABEL



12.3.2 CERTIFICATE OF ANALYSIS

Because efficacy matters.™

3017 Business Park Drive, Stevens Point, WI 54482
Phone: 877-342-9881 Fax: 715-342-9866

CERTIFICATE OF ANALYSIS

PRODUCT NAME:	Vitamin D3 50000 IU	**MANUFACTURED DATE:**	2-21-20
PRODUCT#:	103B	**EXPIRATION DATE:**	6-22
WIP LOT#:	83654		

IDENTITY ANALYSIS	SPECIFICATION	RESULT	METHOD	PASS/FAIL
	Spectral Identification	Conforms	MOP 10431	PASS
	Organoleptic Identification	Conforms	MOP 10430	PASS

WEIGHT VARIATION TESTING	SPECIFICATION	RESULT	METHOD	PASS/FAIL
	0.475 - 0.595 g	0.499 g	MOP 10183	PASS

ONE CAPSULE CONTAINS

Active Ingredients	SPECIFICATION	RESULT	METHOD	PASS/FAIL
Vitamin D	1250 - 1500 mcg (50000-60000 IU)	50500 IU	MOP 10390	PASS

MICRO TESTING	SPECIFICATION	RESULT	METHOD	PASS/FAIL
E. coli	Absent in 10 grams	Complies	MOP 10281	PASS
Staphylococcus	Absent in 10 grams	Complies	MOP 10281	PASS
Salmonella	Absent in 10 grams	Complies	MOP 10281	PASS

CREATED BY/DATE: Mark Merucci 4-1-2020
Mark Merucci
Technical Research Associate

12.3.3 STABILTY REPORT

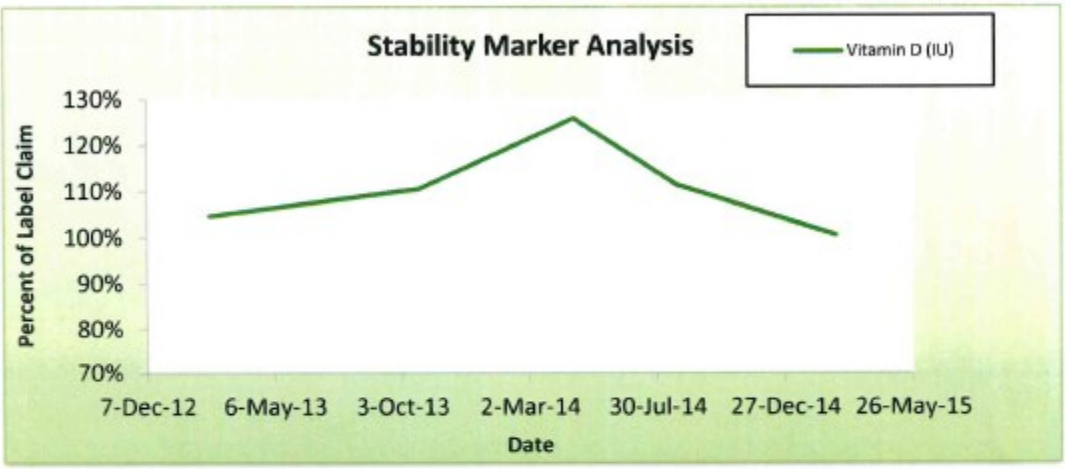
Product Name: Vitamin D 50,000

Item#: 103 Manufacture Date: 20-Feb-13

Lot#: 74444 Expiration Date: 12-Feb-15

ORTHO MOLECULAR PRODUCTS
Because Efficacy Matters

Stability Marker Analysis



Marker: Vitamin D (IU) Label Claim: 50000

Test Date:	19-Feb-13	23-Oct-13	23-Apr-14	22-Aug-14	25-Feb-15
Result (dosage units):	52298	55218	62879	55692	50196
Percent of Label Claim:	105%	110%	126%	111%	100%

Microbiological Analysis

Test Date	E.coli	Salmonella	Staphylococcus
20-Feb-13	pass	pass	pass
25-Feb-15	pass	pass	pass

Report Conclusion

Product met label claim up to the expiration date. Study is supportive of the current (24 month) expiration period.

Report Completed By/Date: Kelly Miller 4-27-15

QA Reviewed By/Date: [signature] 4-27-15

12.3.4 GMP CERTIFICATION

NSF INTERNATIONAL

789 N. Dixboro Road, Ann Arbor, Michigan 48105 USA
+1 800 673 6275

GMP Registered
Dietary Supplements

NSF International has assessed and confirmed compliance of

Provident Nutraceutical - a division of Ortho Molecular Products Inc.

Facility: 3017 Business Park Drive, Stevens Point, WI, 54481, United States

to NSF GMP Registration Program Requirements of NSF/ANSI 173, Section 8
which includes FSMA and cGMP (21 CFR 111), (21 CFR 117)

Print Date:	January 03, 2020
Certificate Number:	C0242769-DS-1
Initial Certification:	July 13, 2015
Expiration Date:	August 06, 2020

David Trosin
General Manager,
Health Sciences Certification

This certificate is the property of NSF International and must be returned upon request. For the most current and complete information, please access NSF's website (www.nsf.org).

12.4 SAMPLE PATIENT PACKET ITEMS

12.4.1 SAMPLE DRUG DIARY

Front Page

DOSING LOG

Supplement for COVID-19

One the first day only, you will take TWO 1.25mg (2.5mg total) Vitamin D capsules.

On days 1-15 you will take TWO capsules of the supplement FOUR times per day
Please indicate the date, time, amount taken and any comments.

		Dose Taken				
	Date	1st dose	2nd dose	3rd dose	4th dose	Comments
Ex:	6/1/2020	x	x		x	vomited 3rd dose
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						
Day 8						
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						
Day 15						

If you have questions about your medical condition, contact your primary care provider.
If you are having a medical emergency, go to the nearest emergency department.

Study Participant
Self-Administration
Study Drug Diary

Participant Identifier: _____

Protocol # : 200412-4

STUDY DRUG INSTRUCTIONS:

Study Drug: Supplement for COVID-19
How Much: 2 capsules 4 times per day
How Often: Take with meals and at bedtime
When: There should be 4-6 hours between doses.

SPECIAL INSTRUCTIONS:
Take with food. Best absoption expected with 15-20 gm of fat per meal

If you have difficulty swallowing pills, contents of capsules can be mixed with food. (eg: yogurt, applesauce, peanut butter)

Keep out of sunlight. Store at room temperature. Avoid excess heat.

Keep supplement in original container

If you have questions about the study, please email us at supplement3covid19@gmail.com or call 614-5-COVID-2 (leave a message if there is no answer).

Back Page

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

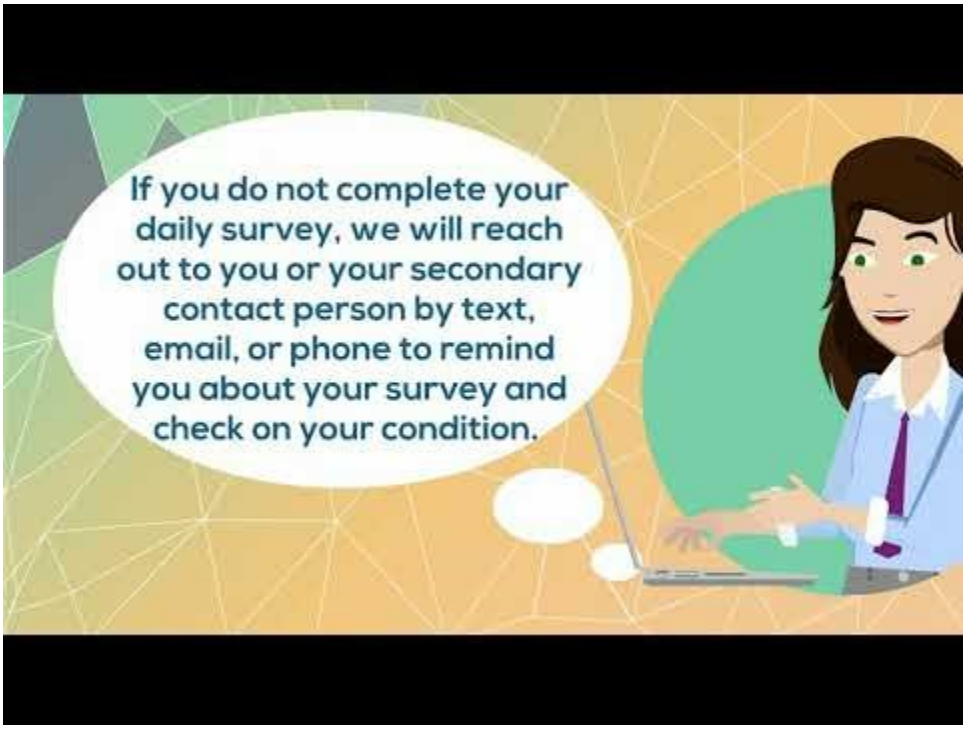
Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

We will ask you to report your symptoms and side effects on day 1, 8, and 15 via an online questionaire.

Symptom	Start Date	End Date	Severity

12.5 WELCOME VIDEO



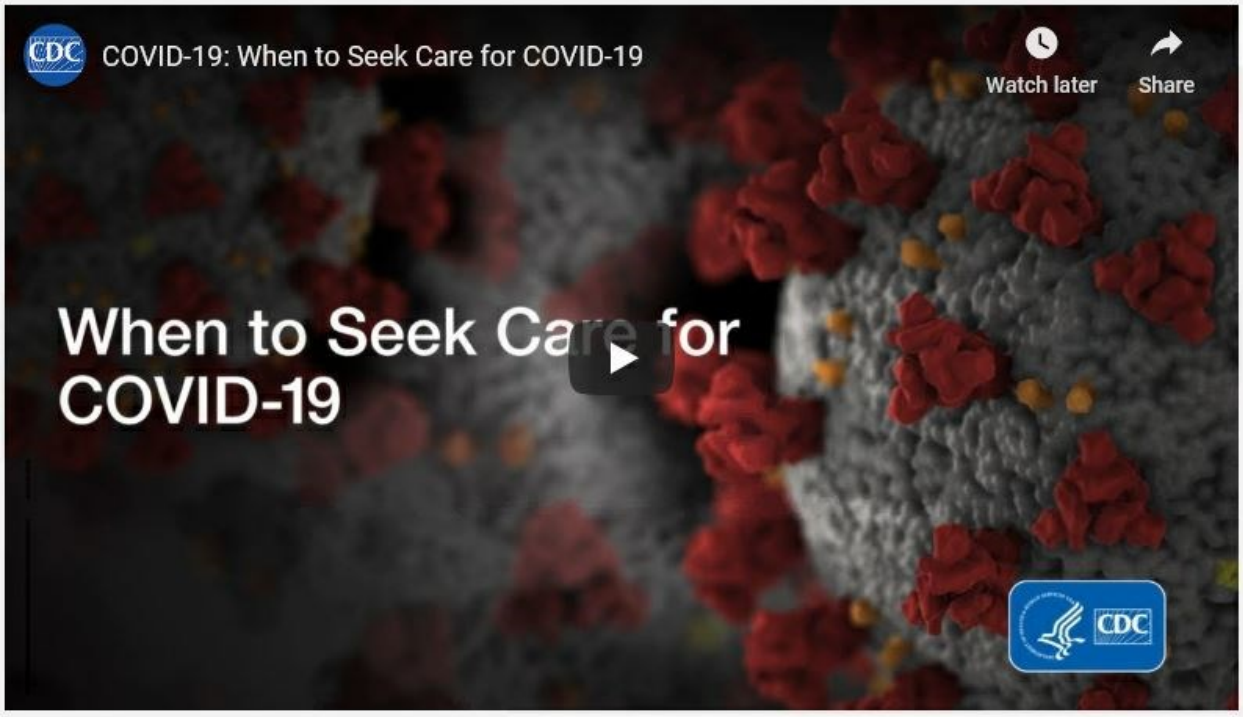
https://www.youtube.com/embed/0bVxe1KlAy4?feature=oembed

12.6 PATIENT SURVEYS

12.6.1 – DAILY QUESTIONNAIRE

Data entered on the form might not be seen by the researchers for several days. If you have concerns about your current condition, call your primary care provider or the Ohio Department of Heath hotline at 1-833-4-ASK-ODH. If you are having a medical emergency, go to your nearest emergency department or call 911.

When to seek care for COVID-19



If you develop emergency warning signs for COVID-19 get medical attention immediately. Emergency warning signs include*:

Trouble breathing
Persistent pain or pressure in the chest
New confusion or inability to arouse
Bluish lips or face

***This list is not all inclusive. Please consult your medical provider for any other symptoms that are severe or concerning.**

For non-urgent questions, more information can be found at:
https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html

These are DRAFT example questions. Questions will be finalized before patient enrollment.

Note that questions will be formatted for electronic viewing and will have conditional formatting such that only relevant questions will be visible.

Confidential

Symptom Diary

Study ID _____

Our goal is for you to take 8 capsule divided over the course of the day, such as 2 capsules with each meal (breakfast, lunch, dinner), and again at bedtime. If you miss one dose, you can divide the missed dosage amongst the next 2 dose. For example, if you missed the breakfast dose, you can take 3 with lunch, 3 with dinner, and 2 at bedtime. You should take the capsules with some food or snack. You are more like to have an upset stomach with 3 capsules than 2 capsules. Although you are likely to have no adverse effects either way. If you notice that the capsules give you an upset stomach, be sure to take them with food.

Medication diary
[study_id]

Please refer to the paper diary sheet, how many capsules did you take yesterday? (If you took all of 4 doses, you would have taken 8 capsules).

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9

(We understand that remembering to take pills 4 times a day can be difficult, and we understand that some doses may get missed. It is important for us to understand if missed doses will make difference in the results.)

Symptom Diary

	Yes	No	Unknown
Fever >100.4F (38C)	◯	◯	◯
Subjective fever (felt feverish)	◯	◯	◯
Chills	◯	◯	◯
Muscle aches (myalgia)	◯	◯	◯
Runny nose (rhinorrhea)	◯	◯	◯
Sore throat	◯	◯	◯
Cough (new onset or worsening of chronic cough)	◯	◯	◯
Shortness of breath (dyspnea)	◯	◯	◯
Nausea or Vomiting	◯	◯	◯
Headache	◯	◯	◯
Abdominal pain	◯	◯	◯
Diarrhea (>3 loose/looser than normal stools/24hr period)	◯	◯	◯

What's your highest temperature within the past 24 hours? (If you have access to a thermometer)

_____
(Farenheight temperature)

Confidential

Overall how do you feel compared to yesterday?	Much worse — Same — Much better (Place a mark on the scale above)
TODAY, what was the SEVERITY of your SHORTNESS OF BREATH, at its WORST	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
TODAY, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
TODAY, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
TODAY, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
TODAY, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?	◯ Never ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
Other symptoms - 1	◯
Other symptoms - 1, specify:	_____
Other symptoms - 2	◯
Other symptoms - 2, specify:	_____
Other symptoms - 3	◯
Other symptoms - 3, specify:	_____
Have you had to seek medical attention in the past 24 hours?	☐ Yes, called a help line ☐ Yes, when to an urgent care / emergency department. ☐ Yes, I was admitted to the hospital ☐ None of the above ☐ Other
Other:	_____

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Have you have any other medical events within the past 24 hours (not previously reported)? This could include items not necessarily related to COVID-19, such as a car accident, broken bone, or new/worsening of another medical condition.	

National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases

12.6.2 – PRO-CTCAE QUESTIONNAIRE (DAY 1, 8, & 15, 21, 30, AND 60)

These are DRAFT example question. Questions will be finalized before patient enrollment

Note that questions will be formatted for electronic viewing and will have conditional formatting such that only relevant questions will be visible.

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Resveratrol for COVID-19
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PRO-CTCAE

Study ID _____

As patients go through their illness, they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days...

In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the SEVERITY of your SORE THROAT or MOUTH SORE their WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the SEVERITY of your HOARSE VOICE at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING OR SMELLING at their WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how OFTEN did you have NAUSEA?	◯ Never ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe

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In the last 7 days, how **OFTEN** did you have **VOMITING**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **VOMITING** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how **OFTEN** did you have **HEARTBURN**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **HEARTBURN** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, did you have any **INCREASED PASSING OF GAS (FLATULENCE)**?	◯ Yes ◯ **N**o
In the last 7 days, how **OFTEN** did you have **BLOATING OF THE ABDOMEN (BELLY)**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **BLOATING OF THE ABDOMEN (BELLY)** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how **OFTEN** did you have **LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **CONSTIPATION** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how **OFTEN** did you have **PAIN IN THE ABDOMEN (BELLY AREA)**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly

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In the last 7 days, what was the **SEVERITY** of your **PAIN IN THE ABDOMEN (BELLY AREA)** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, what was the **SEVERITY** of your **SHORTNESS OF BREATH** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did your **SHORTNESS OF BREATH INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, what was the **SEVERITY** of your **COUGH** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **COUGH INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, what was the **SEVERITY** of your **WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING)** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how **OFTEN** did you feel a **POUNDING OR RACING HEARTBEAT (PALPITATIONS)**?	◯ Never ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, did you have any **RASH**?	◯ Yes ◯ No
In the last 7 days, what was the **SEVERITY** of your **ITCHY SKIN** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, did you have any **HIVES (ITCHY RED BUMPS ON THE SKIN)**?	◯ Yes ◯ No

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In the last 7 days, what was the **SEVERITY** of your **DIZZINESS** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the **SEVERITY** of your **BLURRY VISION** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **BLURRY VISION INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, what was the **SEVERITY** of your **REDNESS** or **WATERY EYES (TEARING)** at their **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, what was the **SEVERITY** of your **PROBLEMS WITH CONCENTRATION** at their **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **PROBLEMS WITH CONCENTRATION INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, what was the **SEVERITY** of your **PROBLEMS WITH MEMORY** at their **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **PROBLEMS WITH MEMORY INTERFERE** with your usual or daily activities?	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, how **OFTEN** did you have **PAIN**?	◯ Never ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **PAIN** at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe

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In the last 7 days, how much did **PAIN INTEREFERE** with your usual or daily activities?	◯ **N**ot at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, how **OFTEN** did you have a **HEADACHE**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **HEADACHE** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did your **HEADACHE INTERFERE** with your usual or daily activities?	◯ **N**ot at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, how **OFTEN** did you have **ACHING MUSCLES**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **ACHING MUSCLES** at their **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **ACHING MUSCLES INTEREFERE** with your usual or daily activities?	◯ **N**ot at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, how **OFTEN** did you have **ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)** at their **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE** with your usual or daily activities?	◯ **N**ot at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much

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In the last 7 days, what was the **SEVERITY** of your **FATIGUE, TIREDNESS, OR LACK OF ENERGY** at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how much did **FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE** with your usual or daily activities?	◯ **N**ot at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the last 7 days, did you **BRUISE EASILY (BLACK AND BLUE MARKS)**?	◯ Yes ◯ **N**o
In the last 7 days, how **OFTEN** did you have **NOSEBLEEDS**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **NOSEBLEEDS** at their **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
In the last 7 days, how **OFTEN** did you have **SHIVERING OR SHAKING CHILLS**?	◯ **N**ever ◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost constantly
In the last 7 days, what was the **SEVERITY** of your **SHIVERING OR SHAKING CHILLS** at their **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
Do you have any other symptoms that you wish to report?	◯ Yes ◯ **N**o
Please list another symptom you would like to report (symptom 1):	_____
In the last 7 days, what was the **SEVERITY** of this (symptom 1 above) symptom at its **WORST**?	◯ **N**one ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
Please list another symptom you would like to report (symptom 2):	_____

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In the last 7 days, what was the **SEVERITY** of this (symptom 2 above) symptom at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
Please list another symptom you would like to report (symptom 3):	_____
In the last 7 days, what was the **SEVERITY** of this (symptom 3 above) symptom at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
Please list any other symptom you would like to report (symptom 4):	_____
In the last 7 days, what was the **SEVERITY** of this (symptom 4 above) symptom at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe
Please list another symptom you would like to report (symptom 5):	_____
In the last 7 days, what was the **SEVERITY** of this (symptom 5 above) symptom at its **WORST**?	◯ None ◯ Mild ◯ Moderate ◯ Severe, ◯ Very Severe

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