Evaluation of zinc and green tea extract supplementation on reduction in symptom duration and severity associated with community respiratory viral infections: a randomized control trial (ZiPhenol Study)

Protocol Number: 1

National Clinical Trial (NCT) Identified Number: 04898023

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IND Number: 152998

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23 February 2023

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 6.1	Removed EGCG dosing information	IRB requested to remove EGCG dosing detail as amount from the wholesaler green tea extract product is described as ≥50% EGCG vs an exact amount.
4.1, 6.2	Added 'or designated pharmacist' when describing duties of IDS staff	This added language was requested by IDS staff so to capture the use of other MUHC pharmacists for after-hours dispensing operations if needed.
4.3	Updated mg/capsule of elemental zinc	Back updating text within this section to reflect compounding changes made in an earlier protocol version (v1.4).

6.1, 6.2	**Changed fill weight target of placebo capsules to 300mg ± 10%**	**Following the preparation of several batches of placebo capsules to-date it has been observed that there is a relatively high rate of poor capsulation (i.e. rejected capsules) of these capsules leading to waste of the microcrystalline cellulose material used to make them as well as the empty capsule supply on hand. Lowering fill weight helps improve the yield of successful placebo capsules made during the capping process thus warranting a protocol update. The microcrystalline cellulose material is inert and possesses no pharmaceutical activity thus lowering the fill weight of placebo capsules is immaterial to study outcome measures.**
6.1	**The zinc citrate per capsule amount was added to the elemental zinc amount description**	**This additional detail was requested by IDS staff.**
6.2	**Changed beyond-use date from 30 days to 180 days**	**Initial selection for the beyond-use date was based on guidance from the Missouri Board of Pharmacy, which recommended use of clinical judgement. As such, a very conservative (and arbitrary) short dating of 30 days was used. Due to slower than expected enrollment this has led to several batches of study product having to be wasted. IDS staff recommended using the United States Pharmacopeia (USP) 795 standards for non-sterile compounding instead of the Missouri Board guidance. USP states more definitely the beyond-use date for compounded solid dosage forms can be up to 180 days.**
6.2	**Removed language 'at the direction of the primary investigator'**	**This removal was requested by IDS staff as their standard operating procedures includes routine disposal of unused study drug without notifying the primary investigator.**

10.1	**Updated structure of Independent Safety Monitor (ISM)**	**ISM personnel description updated to reflect current personnel; frequency of monitoring changed to percentages of enrollment target to accommodate the slower than anticipated enrollment.**

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STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the University of Missouri School of Medicine Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent form needs to be obtained from participants who provided consent, using a previously approved consent form.

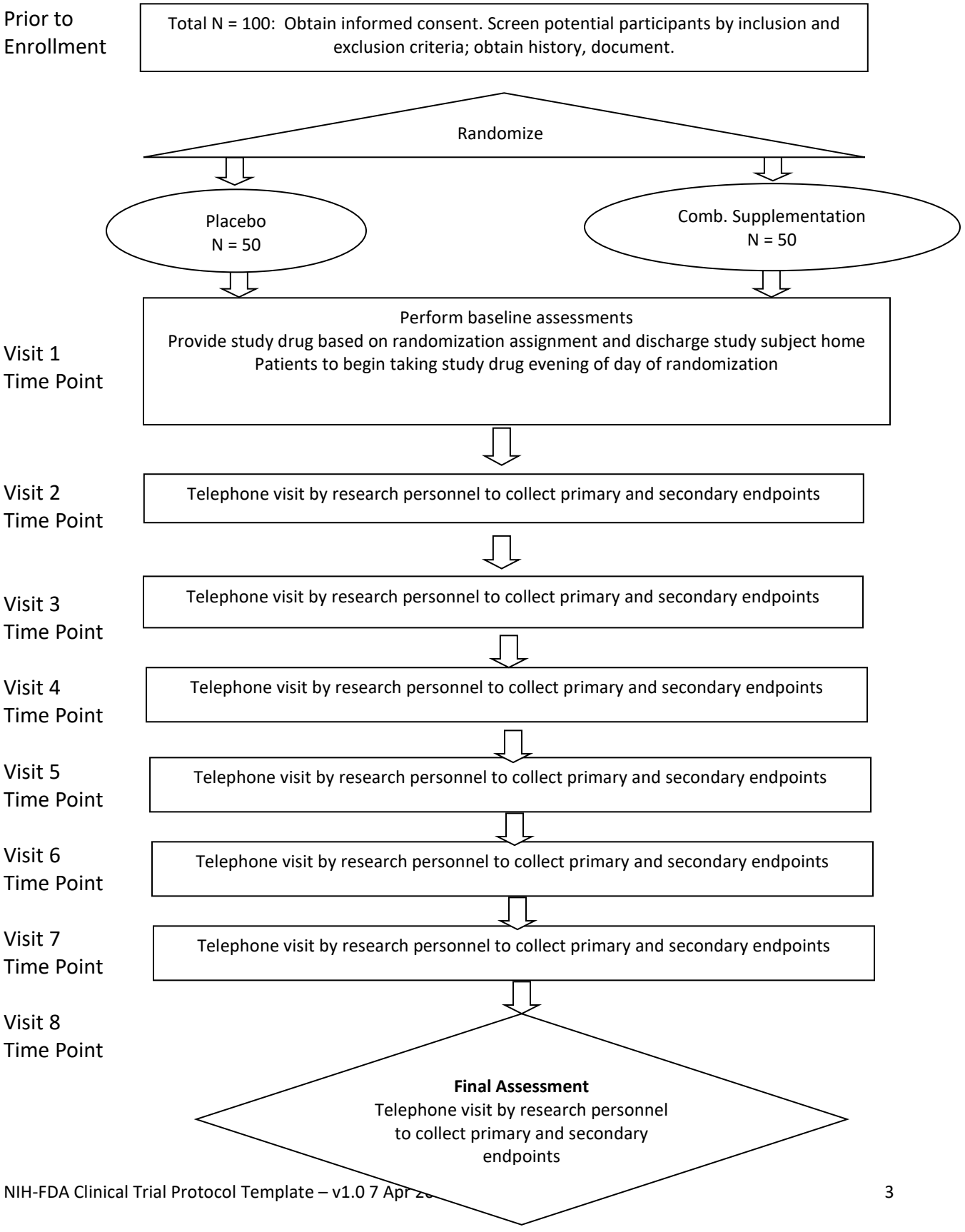
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Evaluation of zinc and green tea extract supplementation on reduction in symptom duration and severity associated with community respiratory viral infections: a randomized control trial (ZiPhenol Study)
Study Description:	Zinc and green tea supplementation have both been independently studied for supporting immune health during cold and flu-like illness in non-hospitalized patients with clinical trials demonstrating promising but inconsistent results. However, combination therapy may offer an improved effect as the antioxidant compound, epigallocatechin gallate (EGCG), found in green tea has been demonstrated in-vitro to increase intracellular concentrations of free zinc. Elevation of intracellular zinc is associated with inhibition of RNA-dependent RNA polymerase, which is the enzyme required for viral replication in the host cell. This study seeks to evaluate the effect of combination supplementation using established doses of zinc and green tea extract (EGCG) on symptom duration and severity from cold and flu-like illness, including COVID-19, in adult community patients enrolled in a randomized placebo-controlled trial.
Objectives:	Primary Objective: Determine the impact of combination supplementation against placebo on symptom duration and severity in non-hospitalized adult patients acutely infected with a respiratory viral illness Secondary Objectives:

	1. Compare adverse events of combination supplementation against placebo 2. Compare patient-reported morbidity events of days missed from work or school and hospitalization or physician office visit(s) for respiratory viral illness related complications associated with combination supplementation versus placebo
Endpoints:	Primary Endpoint: Rate of recovery from cold and flu-like symptoms will be determined by quantifying the proportion of patients achieving a daily total symptom severity score of 0 or 1 using an established 12 symptom scoring system with a severity scale ranging from 0-absent to 3-very severe for each symptom (max of 36 points) through seven days of follow-up. Secondary Endpoints: 1. Rates of patient-reported adverse events including nausea, vomiting, indigestion, worsening of shortness of breath or difficulty breathing, allergic reaction including skin rash, and need to seek medical care (e.g. hospitalization or physician visit) for a suspected study drug related adverse effect 2. Rates of patient-reported days missed from work or school and hospitalization or physician office visit(s) for respiratory viral illness related complications
Study Population:	100 patients aged 18 years and older seeking medical care at University of Missouri Health Care Emergency Department for cold and flu-like illness will be targeted for enrollment. Men and women of all ethnicities will be included.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	University of Missouri Health Care (MUHC) is a Level 1 Trauma Academic Medical Center in central Missouri with over 600 staffed beds. The Emergency and Trauma Center experiences nearly 80,000 patient visits each year from a diverse population and has a dedicated research center that conducts a broad range of research initiatives. Currently, over 30 publications have been indexed by PubMed from the MUHC Emergency Medicine Department.
Description of Study Intervention:	Enrolled patients will be randomized (1:1) to either placebo or combination supplementation consisting of zinc 33mg, green tea extract 267mg, and ascorbic acid 67mg each per capsule. Study subjects will be instructed to take three (3) capsules of either placebo or combination supplementation two (2) hours following a meal twice daily for five days. Patients will be followed-up for a period of seven consecutive days following randomization.
Study Duration:	May 30, 2022 - June 1, 2023
Participant Duration:	8 days (including day of enrollment)

1.2 SCHEMA


Prior to Enrollment
Total N = 100: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Placebo
N = 50
Comb. Supplementation
N = 50
Visit 1
Time Point
Perform baseline assessments
Provide study drug based on randomization assignment and discharge study subject home
Patients to begin taking study drug evening of day of randomization
Visit 2
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 3
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 4
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 5
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 6
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 7
Time Point
Telephone visit by research personnel to collect primary and secondary endpoints
Visit 8
Time Point
Final Assessment
Telephone visit by research personnel to collect primary and secondary endpoints

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/Enrollment/ Baseline Visit 1, Day 1		Study Visit 2, Day 2	Study Visit 3, Day 3	Study Visit 4, Day 4	Study Visit 5, Day 5	Study Visit 6, Day 6	Study Visit 7, Day 7	Study Visit 8, Day 8
Informed consent	X								
Demographics±	X								
Medical history±	X								
Randomization	X								
Administer study intervention	X----------X								
Daily telephone visits for collection of study endpoints	X----------X								
Concomitant medication review	X----------X								
Physical exam (including height and weight) ±	X								
Vital signs±	X								
Height±	X								
Weight±	X								
Hematology ±	X								
Serum chemistry± a	X								
EKG (as indicated) ±	X								
Adverse event review and evaluation	X----------X								
Radiologic/Imaging assessment±	X								
Other assessments (e.g., immunology assays, pharmacokinetic) ±	X								

± - Indicates procedures done as part of routine care and not specific to study methods

a – Basic metabolic panel or complete metabolic panel

2 INTRODUCTION

2.1 STUDY RATIONALE

RNA viruses are common causes of respiratory infections in humans with limited treatments available, especially non-prescription options. Zinc and green tea supplementation have both been independently studied for supporting immune health during cold and flu-like illness in non-hospitalized patients with clinical trials demonstrating promising but inconsistent results. However, combination therapy may offer an improved effect as the antioxidant compound, epigallocatechin gallate (EGCG), found in green tea has been demonstrated in-vitro to increase intracellular concentrations of free zinc. Elevation of intracellular zinc is associated with inhibition of RNA-dependent RNA polymerase, which is the enzyme required for viral replication in the host cell. This study aim seeks to evaluate the effect of combination supplementation using established doses of zinc and green tea extract (EGCG) on symptom duration and

severity from cold and flu-like illness, including COVID-19, in community patients enrolled in a randomized placebo-controlled trial.

2.2 BACKGROUND

RNA viruses (e.g. rhinovirus, influenza, coronavirus, etc.) are common causes of respiratory infections in humans contributing to significant morbidity. It is estimated that over 500 million non-influenza respiratory infections occur each year in the U.S costing $40 billion annually due to absenteeism and healthcare related expenditures.[1] This disease burden has significantly increased in recent months as COVID-19 continues to impact patients across the world with over 7 million U.S. cases at the time of this writing.[2] Currently, no Food and Drug Administration (FDA) approved oral therapy exists for preventing or treating non-influenza respiratory viral infections including COVID-19 thus the urgent need for research in developing new therapeutic options.

The COVID-19 pandemic has galvanized the medical community to innovate treatment options in real-time with little historical drug therapy experience to guide decision-making. Early attempts to manage the disease included repurposing existing FDA approved drug therapy with conflicting results. Among these agents included the antimalarial drugs chloroquine and hydroxychloroquine, azithromycin, and the antiretroviral lopinavir/ritonavir (Kaletra®).[3] In May 2020 the FDA issued an emergency use authorization (EUA) for the intravenous antiviral agent remdesivir for treatment of severe COVID-19.[4] This EUA was expanded to include treatment in all hospitalized patients regardless of disease severity;[4] however, most patients with COVID-19 and other non-influenza respiratory viral illnesses do not require hospital stay leaving them with limited treatment options. Recently the FDA authorized use of newer therapies for COVID-19 in non-hospitalized patients including nirmatrelvir-ritonavir and molnupiravir, however, these are recommended for those only at high risk of progressing to severe disease leaving many healthier patients without options for disease management. This gap in care provides impetus to explore alternative treatment strategies including novel use of over-the-counter (OTC) products and supplements.

Zinc is associated with antiviral activity and has been demonstrated to improve recovery time in non-hospitalized patients with an acute viral respiratory illness.[5] This effect is thought to be dependent on the availability of free or ionized zinc (iZn) released from the dosage form,[6] and it has been observed that viral replication is inhibited in-vitro following increases in *intracellular* free zinc.[7,8,9,10] However, ionized zinc is poorly permeable through the cell membrane and a high degree of variability exists between currently available zinc supplements in terms of free zinc bioavailability.[11] Inconsistent real-world results with current over-the-counter (OTC) zinc lozenge products and other dosage forms warrant further investigation into approaches to overcome some of these limitations of zinc supplementation.

Green tea extract (GTE) is a commonly found dietary supplement with a variety of purposes for improving human health including weight loss, anti-inflammatory, cancer prevention, and cardiovascular health.[12] Recently, few published and unpublished data described here indicate the ability of the primary catechin compound found in GTE, epigallocatechin-3-gallate (EGCG), to act as an effective zinc

ionophore.[13,14] This activity has been demonstrated in-vitro using human embryonic kidney cells (HEK293) and concentrations of EGCG (0.1 - 1.5 µM) achievable with established doses for human consumption (figure 1, unpublished data), and appears to be dependent on the extracellular zinc concentration (figure 2, unpublished data).

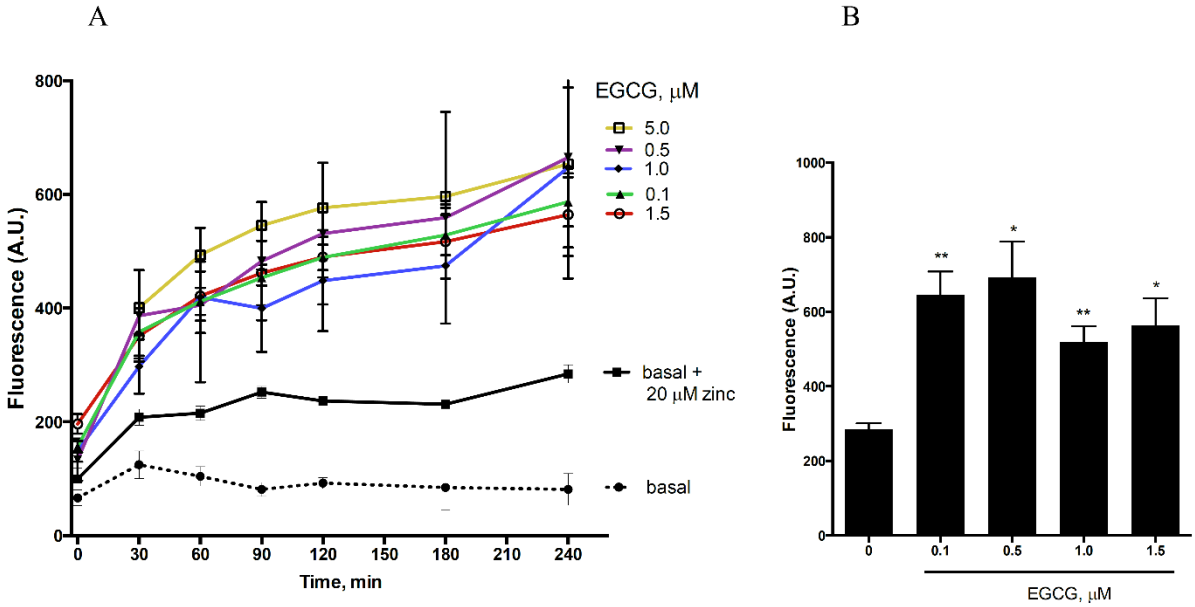


Figure 1 Epigallocatechin-3-gallate (EGCG) increases intracellular labile zinc (Zn) levels
A. HEK293 cells pre-loaded with 1 µM FluoZin-3 were incubated in assay buffer containing no added Zn (basal) or in buffer containing 20 µM Zn with 0.0, 0.1, 0.5, 1.0 or 1.5 µM EGCG. Arbitrary units (A.U.) of fluorescence were measured on a Perkin Elmer plate reader at times indicated. **B.** Statistical analysis of the 240 min time point where *P < 0.05; **P < 0.01 represent significance of EGCG treatments compared with buffer containing 20 µM Zn only.

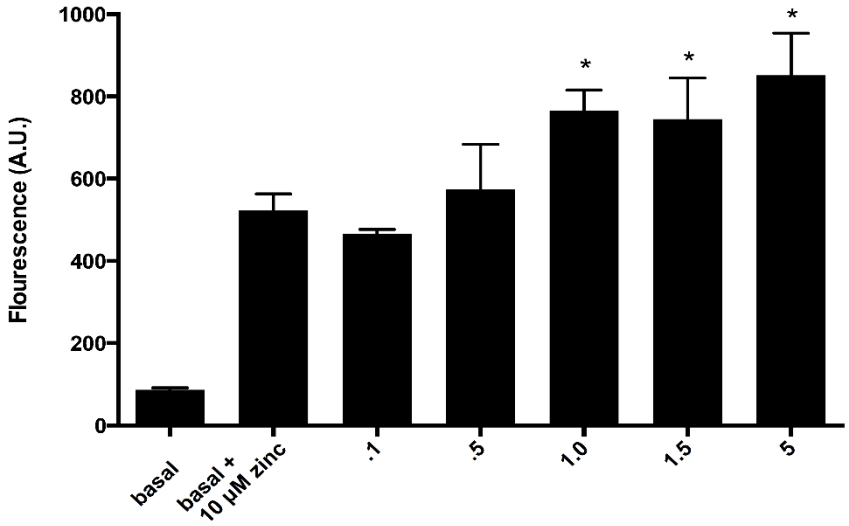


Figure 2 Higher concentrations of EGCG required to increase intracellular Zn when basal Zn is lower
HEK293 cells pre-loaded with 1 µM FluoZin-3 were incubated in assay buffer containing no added Zn (basal) or in buffer containing 10 µM Zn with 0.0, 0.1, 0.5, 1.0, 1.5, or 5.0 µM EGCG. Arbitrary units (A.U.) of fluorescence were measured on a Perkin Elmer plate reader at 240 minutes. Statistical analysis of the 240 min time point where *P < 0.05.

The ability of EGCG to increase intracellular zinc for up to four hours in cell culture may translate to an improved effect of zinc supplementation in-vivo within the clinical context of an acute viral respiratory illness. This concept has been popularized following the COVID-19 pandemic with treatment protocols including hydroxychloroquine/chloroquine and zinc sulfate demonstrating mixed results and has prompted the development of several ongoing clinical studies.[15] Previous clinical investigations of EGCG for non-COVID-19 viral illness have been limited to prevention of cold and flu-like infections with promising results.[16,17] However, combination with zinc supplementation was not evaluated nor were patients with active viral infection enrolled in these studies. Currently, only one active study could be identified on clinicaltrials.gov that seeks to investigate the effect of EGCG on COVID-19 illness.[18] This study did not include concomitant zinc supplementation nor did it evaluate the effect of supplementation on an acute infection.

Ascorbic acid is a well-known supplement often promoted for immune health during the cold and flu season despite inconsistent clinical data supporting its use in this manner. However, in the context of the proposed study supplement, ascorbic acid is intended to be used to enhance EGCG bioavailability as previously described in the literature.[19,20,21,22] A similar approach will be used to formulate the zinc and EGCG combination supplement as described within this study protocol.[23]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk to study subjects is anticipated to be in accordance with those associated with using the study drug components individually. The most common side effect expected is nausea as a 12-month clinical trial evaluating EGCG against placebo using a dosing scheme similar to the current proposal found an incidence of 10.2% vs. 4.8%, respectively.[24] Taking study drug two hours following a meal is expected to limit nausea, but residual risk cannot be eliminated altogether. Secondly, hepatotoxicity has been reported with EGCG supplementation, but risk is associated with treatment durations beyond 2-4 weeks and doses higher than 800 mg/day.[25,26] Our protocol includes only five days of treatment at a dose of 800 mg/day thus liver injury is not an anticipated risk to patients. Furthermore, patients with a history of chronic liver disease will be excluded. Zinc supplementation at the proposed doses may also contribute to increased risk a nausea/vomiting. A case report of severe nausea and vomiting occurred in a 17-year-old male 30 minutes following an acute ingestion of 570mg elemental zinc; however, no other complications were observed.[27] Clinical studies evaluating zinc lozenges for the treatment of cold and flu-like illness have reported increased incidence of gastrointestinal upset as compared to placebo. One such trial using a total daily elemental zinc dose up to 207mg observed a rate of nausea and stomach distress of 13.5% with zinc vs 10.7% that was associated with placebo.[28] No studies of zinc lozenge therapy for cold and flu have reported any serious adverse effects,[5] however, long-term use of zinc supplementation has been associated with copper and iron deficiency.[29] Although the current protocol includes only five days of treatment patients with a history of copper or iron deficiency will be excluded.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits of this study include elucidation of a novel combination of common dietary supplements to improve immune health during an acute respiratory viral illness in non-hospitalized patients. Positive results would be supportive to bring such a combination product to market with the intent to be used during an active infection as opposed to prevention. Most OTC remedies and herbal supplements are marketed for immune health as a preventative strategy, but few options exist for patients that are acutely ill. Common cough and cold products available to patients during an active infection are designed to only reduce severity of symptoms as opposed to improving immune health with the goal of shortening the disease process. This gap in care is of significance as it is estimated that over 500 million non-influenza respiratory infections occur each year accounting for $40 billion annually in direct and indirect costs stemming from absenteeism and health-care related expenditures.[1]

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk-benefit assessment of this study intervention is considered favorable given the unmet clinical need for alternative therapies to help reduce the disease burden of community respiratory viral infections, including COVID-19. The study drug components are each a well-known dietary supplement with established dosing ranges and side effect profiles and are already individually used to help prevent or reduce cold and flu-like symptoms. Combination supplementation has not been evaluated in the method being proposed, but the additive risk of nausea is expected. The administration of study drug

two hours after a meal is anticipated to lower gastrointestinal disturbance, and the short duration of therapy planned will limit any possible long-term adverse effects associated with the higher doses of zinc and EGCG being used.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the impact of combination supplementation against placebo on symptom duration and severity in non-hospitalized adult patients acutely infected with a respiratory viral illness, including COVID-19	Rate of recovery from cold and flu-like symptoms defined as achieving a daily total symptom severity score of 0 or 1 within 7 days using an established 12 symptom scoring system with a severity scale ranging from 0-absent to 3-very severe for each symptom (max of 36 points). The 12 symptom domains include: nasal drainage, nasal congestion, sneezing, scratchy throat, sore throat, cough, headache, hoarseness, muscle ache, shivering or feverish, tiredness and difficulty in concentration. Mean total symptom severity scores and time to recovery will be compared between groups. The follow-up period will be seven consecutive days following randomization.	The primary outcome is derived from established clinical trial methodology evaluating the effectiveness of zinc supplementation for cold and flu-like illness. We selected this measure to maintain consistency within the published literature and to best assess patient relevant outcomes.
Secondary		
1. Compare adverse events of combination supplementation against placebo 2. Compare patient-reported morbidity events of days missed from work or school and hospitalization or physician office visit(s) for respiratory viral illness related complications associated with combination supplementation versus placebo	1. Rates of patient-reported adverse events including nausea, vomiting, indigestion, worsening of shortness of breath or difficulty breathing, allergic reaction including skin rash, and need to seek medical care (e.g. hospitalization or physician visit) for a suspected study drug related adverse effect 2. Rates of patient-reported days missed from work or school and hospitalization or physician office	Relevant safety endpoints were selected from established clinical trials assessing zinc and EGCG supplementation individually. Morbidity events of missed days from work or school or need to seek medical care for worsening respiratory illness is relevant to assess the

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	visit(s) for respiratory viral illness related complications	difference in disease burden between supplementation and placebo.
Tertiary/Exploratory		
Determine the impact of combination supplementation against placebo on symptom duration and severity in the COVID-19 positive subgroup of enrolled patients	Rate of recovery from cold and flu-like symptoms defined as achieving a daily total symptom severity score of 0 or 1 within 7 days using an established 12 symptom scoring system with a severity scale ranging from 0-absent to 3-very severe for each symptom (max of 36 points). The 12 symptom domains include: nasal drainage, nasal congestion, sneezing, scratchy throat, sore throat, cough, headache, hoarseness, muscle ache, shivering or feverish, tiredness and difficulty in concentration. Mean total symptom severity scores and time to recovery will be compared between groups.	This exploratory outcome is of interest given the continuous efforts to improve the management of COVID-19 associated disease, and advance the medical knowledge on possible remedies to better improve outcomes in non-hospitalized patients. Positive findings would garner interest to design a randomized control study exclusivity enrolling COVID-19 patients

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a double-blind, placebo-controlled, randomized phase 2 study evaluating the combination of zinc citrate, green tea extract, and ascorbic acid supplementation given for five days on reduction in symptom duration and severity associated with an acute community respiratory viral infection, including COVID-19. Patients presenting to MUHC emergency department (ED) seeking routine care for respiratory viral illness related symptoms will be screened for study eligibility by ED medical staff. A target of 100 eligible patients will be consented and enrolled into the trial by key study personnel in the ED at the time of their visit. A study prescription will be generated by an authorized study team member also at the time of visit and will be sent to the MUHC investigational research pharmacist or designated pharmacist for processing. This will include 1:1 randomization of the study subject to one of the two study arms (n=50 for each arm), filling of prescription with required documentation and labeling, and coordination with ED research services for final dispensing to the patient. Study patients will be discharged from the ED with their study drug before returning home later that day. Due to the time sensitive inclusion criterion necessitating same day study drug dispensing patients seeking medical care

during normal business hours (Monday – Friday; 0800 – 1630) will be targeted for enrollment, however, after hours enrollment may occur based on availability of investigational drug services pharmacy staff or designated pharmacist. Use of a placebo control and treatment blinding is required to limit observer and recall bias given the subjectivity of the outcomes of measure. Patients enrolled will be instructed to discontinue any current OTC products that contain any of the components of the study drug to mitigate confounding of treatment effect. Common cough and cold products that do not share ingredients with study drug will be allowed, and daily utilization will be quantified as name and number of products used and doses of each taken daily. This strategy will allow standard-of-care treatment via patient directed symptom management using traditional OTC cough and cold medicines, while minimizing bias in evaluation of study outcomes. Placebo assignment is assessed to be ethical as no FDA approved therapy for the prevention or treatment of non-influenza respiratory viral illness exists.

A separate study is planned that will collect blood samples in 10 patients to assess serum concentrations of zinc and EGCG, and a complete metabolic panel (CMP) following five days of taking study drug. Baseline serum zinc levels will be collected at time of study enrollment in the MUHC ED while post-treatment serum concentrations of zinc and EGCG will be obtained on the fifth day of taking study drug. Patients will be instructed to report to the MUHC emergency department approximately two hours following taking a dose of study drug to have their blood drawn for the aforementioned testing. CMP assays will be processed locally at MUHC while serum zinc samples will be sent to Mayo Clinic, and EGCG samples will be sent to the University of Missouri Metabolomics Center for analysis. Patients will be selected using the same criteria as those enrolled in the placebo-controlled trial, but will not be randomized to blinded treatment given the logistical requirements necessitating accurate blood sampling. These patients will also not be a part of primary and secondary endpoint collection via daily telephone visits. The purpose of this study is to simply describe peak serum levels of zinc and EGCG following multiple dosing of the study drug, as well as to assess the rate of transaminitis if any is to occur. A separate consent form will be used for this aspect of the research.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

No oral drug therapy or dietary supplement has been FDA approved for the prevention or reduction in symptom duration of non-influenza viral respiratory illness including the 'common cold' and COVID-19. Recently the FDA authorized use of newer therapies for COVID-19 in non-hospitalized patients including nirmatrelvir-ritonavir and molnupiravir, however, these are recommended for those only at high risk of progressing to severe disease leaving many healthier patients without options for disease management. Since no established FDA approved standard-of-care currently exists a placebo-controlled trial presents little to no ethical challenge. Furthermore, the primary and secondary outcomes are self-reported measures by study participants and the subjectivity of these endpoints necessitates a placebo group for statistical comparisons that minimize recall and observer bias.

4.3 JUSTIFICATION FOR DOSE

Zinc Citrate

Zinc is an essential trace element with a wide therapeutic index, and deficiency is common in developing nations and in the elderly (normal range: 10 - 16.8 μM).[30] Zinc deficiency has been associated with

increased pneumonia risk, and supplemental doses greater than 75 mg/day have been associated with a reduction in the duration of the common cold.[31] A total daily dose of elemental zinc up to 207mg given for seven days has been studied in adults with common cold,[28,32] and doses ranging between 100 to 150 mg/day have been administered for months at a time for other indications with few adverse effects reported.[33] A recent study specifically evaluating zinc lozenges (78mg elemental zinc/day) administered for five days for common cold reported side effects of taste disturbances (52%) and dry or sore mouth (24%) that occurred at a greater rate than placebo (7% and 2%, respectively).[34] However, no serious events were reported.

The dose of zinc selected for this study is based on a pharmacokinetic evaluation of serum zinc concentrations over time following oral administration of 45mg elemental zinc provided as gluconate given under fasting, with food, and two hours post meal conditions in ten young healthy volunteers, 23 ± 2 years (mean ± SD) with an average weight of 70 ± 8 kgs.[35] This dose of zinc was able to raise the serum concentration (Cmax) by 2.45 µM from baseline (11 ± 2 µM) when administered two hours after a meal, while no appreciable increase was observed when zinc was administered with food. The selected dose of elemental zinc given as citrate (33 mg/capsule) for the current study is anticipated to raise serum concentrations (Cmax) in a similar fashion and in a dose proportional manner whereby a ~5 µM increase is expected with a doubling of the dose (i.e. 100mg vs 45mg). The 5 µM increase in Cmax is desired as the ability of EGCG to raise intracellular zinc levels appears to be dependent on the extracellular zinc concentration. Unpublished in-vitro data have demonstrated 10 µM zinc necessitating higher concentrations of EGCG to significantly elevate intracellular zinc (figure 2, unpublished data). Assuming patients enrolled have a serum zinc concentration near 10 µM at baseline (based on studies in healthy volunteers and those with viral respiratory disease),[35,36] a higher dose of zinc would be required to achieve serum levels (Cmax) near 20 µM. This higher extracellular zinc concentration would allow for lower concentrations of EGCG to significantly increase intracellular zinc (figure 1, unpublished data), which is desirable given the relatively poor bioavailability of orally administered EGCG. Although zinc gluconate was the form of zinc utilized for pharmacokinetic study, zinc citrate has been demonstrated to display similar characteristics as zinc gluconate in healthy volunteers with comparable bioavailability (61.3% vs 60.9%, respectively).[37]

Zinc toxicity has been rarely reported, but ingestion of 10 - 30 grams of zinc sulfate (2.5 - 7.5 grams of elemental zinc) can be lethal in adults.[38] Chronic intake of 450 - 1600mg daily can cause anemia, copper deficiency, and myeloneuropathies.[38] Total daily exposure of zinc used in the current study proposal is well below these harmful doses and will be limited to five days in duration. Additionally, twice daily dosing would not be expected to lead to systemic accumulation as the elimination half-life of orally administered zinc is 1.1 hours.[35] Elimination of zinc is mostly through the feces therefore renal impairment would not be expected to alter clearance.

<u>Green Tea Extract</u>

EGCG is a polyphenolic compound found predominately in green tea (*Camellia sinesis*), but is also found in other foods including a variety of fruits and nuts albeit in smaller amounts. A 250 mL cup of brewed green tea contains approximately 25 - 60mg of EGCG along with variable amounts of caffeine.[39] Green tea extract is often sold as a dietary supplement containing 50% or more of EGCG by weight and contains little to no caffeine allowing for higher dosing of the antioxidant catechin compounds found in whole plant tea drinks. EGCG displays a wide therapeutic index with doses studied ranging from 150 -

2,400 mg in subjects without serious adverse effects.[40] EGCG is metabolized via methylation by catechol-O-methyltransferase (COMT) as well as degradation by colonic bacteria with metabolites excreted through both urinary and fecal routes. Drug interaction studies have indicated that EGCG is not expected to inhibit the CYP enzymes 1A2, 2D6, 2C9, or 3A4 to any clinically significant degree following repeated doses of 800 mg/day.[41]

Study dosing of EGCG was selected based on published pharmacokinetic data detailing serum concentrations over time following single and multiple doses of 400mg twice daily in healthy volunteers. A single dose of 400mg taken with food corresponded to an average EGCG Cmax of 0.38 ± 0.18 µM, while fasting conditions yielded a mean Cmax of 1.65 ± 0.87 µM in healthy volunteers (average age of 42 years and weight of 75 ± 20 kgs).[42] A multiple dose study evaluating 400mg twice daily taken with food for four weeks demonstrated a mean Cmax of 0.34 ± 0.14 µM in a separate but similar volunteer population indicating little to no accumulation with this dosing schedule.[43] These serum concentrations were simulated in-vitro to establish a dose response curve of EGCG to increase intracellular zinc concentrations (figure 1, unpublished data). Results indicate the ability of obtainable concentrations of EGCG from a dosing schedule of 400mg twice daily to significantly increase intracellular zinc levels in human kidney cells under experimental conditions. The current study proposal will evaluate the effect of this activity in-vivo providing translational evidence for combination supplementation to improve immune health during an acute respiratory viral illness.

Safety and toxicity data on EGCG have been thoroughly summarized by formal drug safety panels including the European Food and Safety Authority (EFSA) and United States Pharmacopeia Convention (USP).[44,45] Common mild side effects reported with standard dosing include gastrointestinal symptoms especially when taken in a fasting state, but rare cases of hepatoxicity have been reported. The EFSA and USP concluded that doses equal to or greater than 800mg of EGCG per day taken for four months or longer are associated with elevations of alanine aminotransferase (ALT) and aspartate transaminase (AST) in a small percentage (less than 10%) of the population.[44,45] The strongest evidence for safety and hepatotoxicity risk of EGCG comes from the Minnesota Green Tea Trial (MGTT).[46] This was a randomized, placebo-controlled, double-blind trial investigating the effects of daily EGCG (843 mg/day) for 12 months in 1075 post-menopausal women. 538 subjects were randomized to EGCG and the difference in biomarkers for the development of breast cancer was compared against placebo (n=537). The most common side effect reported that occurred significantly more often than placebo was nausea (10.2% vs 4.8%, p =0.001), while no differences were seen in rates of serious adverse events (2.2% vs 1.5%). Liver enzyme elevations in patients taking EGCG occurred more frequently compared to placebo (6.7% vs 0.7%, $p < 0.001$), however, the average increase in ALT was only 5.4 U/L and was reversible after stopping therapy. Overall, green tea extracts are generally considered safe for human consumption with liver injury occurring rarely with doses less than or equal to 800 mg/day of EGCG and taken less than two weeks in duration.[44,45]

Ascorbic Acid

Vitamin C is an essential nutrient for human health and must be obtained through dietary supplementation. Clinical uses of ascorbic acid include treatment of scurvy, enhancing absorption of iron, acidification of urine, skin care, and prevention and treatment of the common cold. Although the immunomodulatory properties of vitamin C are favorable the purpose for the proposed study is to enhance absorption of EGCG.[47,48,49,50] This is achieved by combining 200mg of ascorbic acid with

standard and high doses of EGCG, which has been previously described.[51] Safe dosing of vitamin C has been established up to 2000 mg/day where higher doses are associated with diarrhea and gastrointestinal upset.[52] Total daily exposure with the designed dosing protocol (400mg) is well below the recommended daily limit and thus no serious adverse effects are expected.

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. The study period will be terminated early if the IRB, Independent Safety Monitor, or study investigators determine that the study jeopardizes patient safety beyond an expected risk level at any time.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 years and older
4. Ability to take oral medication and be willing to adhere to the prescribed dosing regimen
5. Self-reported cold or flu symptoms for < 72 hours

Men and women of all ethnicities will be included.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant or actively seeking to become pregnant
2. Positive for influenza with planned treatment with oseltamivir or baloxavir
3. Current or planned treatment with an FDA regulated drug (including those under EUA) for COVID-19
4. Chronic liver disease (i.e. baseline liver function tests (LFTs) > 1.5x the ULN or established cirrhosis)
5. Chronic renal failure stage 4 or greater
6. History of kidney stones
7. Acute secondary bacterial infection at the time of enrollment
8. Requiring hospitalization for any reason at the time of enrollment
9. History of copper or iron deficiency
10. Current prescription for quinolone antibiotics, tetracycline antibiotics, or penicillamine at the time of enrollment

11. Allergy/intolerance to any of the active ingredients under investigation including zinc citrate, green tea extract, and ascorbic acid (vitamin C)
12. Patients without decision making capacity
13. Currently enrolled in another clinical trial for a respiratory viral infection

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- discontinue any OTC supplements containing the active ingredients of study treatment beginning the first day of randomization and during the entire follow-up period
- record daily usage of OTC cough and cold preparations with product(s) names and daily doses taken using a 'sick' diary (not required but will be encouraged)

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 positive influenza test with intention to be treated with oseltamivir or baloxavir may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited through the emergency department at MUHC during study months of May 2022 – June 2023. Patients seeking routine care for respiratory viral illness related symptoms will be screened by ED medical staff for eligibility and if appropriate will be consented by key study personnel members for enrollment. The target number of subjects to be enrolled during the study period occurring May 2022 – June 2023 is 100 (50 patients randomized to placebo and 50 to the supplementation group). This target is derived from similarly conducted studies evaluating zinc supplementation (without green tea) in a comparable adult population as identified with the current proposal. The anticipated accrual rate is approximately 5-10 patients each week based on current MUHC ED patient visit volumes and prevalence of cold and flu-like illness during the study time period. MUHC is considered a safety net hospital and therefore treat patients regardless of their insurance status. This designation will allow underrepresented populations equal opportunity to participate in this study. Advertisements will be used including a flyer containing the University of Missouri School of Medicine logo that will be placed in select clinic spaces, and an email announcement distributed through the study site's email system to help increase awareness of study opportunity for interested patients or their caregivers.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The compounded supplementation study product includes select amounts of zinc citrate, green tea extract, and ascorbic acid that have been mixed together using geometric dilution to form a light brown fine powder, and is capsulated using a capsule machine with size 0 empty gelatin capsules resulting in a measured weight of 438mg ± 10% per capsule. The per capsule amount of each supplement component is as follows:

267mg of green tea extract/capsule
104mg of zinc citrate (33mg elemental zinc)/capsule
67mg ascorbic acid/capsule

The finished goods specification sheets, safety data sheets, and certificate of analysis (CoA) for each respective supplement has been provided by the supplier and have been attached as addendums.

Addendum A – zinc citrate specification sheet, safety data sheet, and CoA
Addendum B – green tea extract (≥50% EGCG) specification sheet, safety data sheet, and CoA
Addendum C – ascorbic acid specification sheet, safety data sheet, and CoA

Zinc citrate is a white crystalline powder containing 32% zinc by weight. Zinc is a naturally occurring element that is essential for human health, and various salts are available over-the-counter (OTC) for supplementation purposes. The FDA approved zinc product is zinc sulfate for injection.[53]

Green tea extract is a brown powder-like substance derived from the stems and leaves of *Camellia sinensis* through an extraction process using water and organic solvents such as ethanol. A variety of green tea extracts are available over-the-counter for supplementation and contain little to no caffeine. Extract products contain high amounts of antioxidant catechin compounds the most abundant of which is epigallocatechin-3-gallate (EGCG). The EGCG content of most available green tea extract products is 50% by weight, but variability exists due to inconsistencies in manufacturing processes. The FDA approved a green tea extract product in 2006 called Veregen® (sinecatechins) ointment,[54] which was the first prescription botanical accepted by the governing body.

Ascorbic Acid commonly known as vitamin C is available as a white crystalline powder and available over-the counter for oral supplementation. It is an essential nutrient naturally found in food sources and is FDA approved for the treatment of scurvy.[55]

Placebo capsules will be filled with microcrystalline cellulose, which is refined wood pulp commonly used in food production as an anti-caking or bulking agent. It is a chemically inert compound with no appreciable absorption following oral administration, and has been rarely reported to induce an allergic reaction. The per capsule amount of microcrystalline cellulose is as follows:

300mg ± 10% of microcrystalline cellulose/capsule

The certificate of analysis for microcrystalline cellulose is attached as an addendum.

Addendum D - microcrystalline cellulose CoA

6.1.2 DOSING AND ADMINISTRATION

Eligible patients will be randomized 1:1 to one of the following treatment groups with the following dosing schedule:

1. Zinc/EGCG/ascorbic acid blend: three (3) capsules taken orally two (2) hours following a meal twice daily x5 days.
2. Placebo: three (3) capsules taken orally two (2) hours following a meal twice daily x5 days

The per capsule and total daily dose of each of the individual supplement components is as follows:

267mg green tea extract/capsule (1,600 mg/day)
33mg elemental zinc/capsule (200 mg/day)
67mg ascorbic acid/capsule (400 mg/day)

The per capsule and total daily dose of each of the placebo component is as follows:

300mg microcrystalline cellulose/capsule (1,800 mg/day)

Patients will be instructed to begin taking their assigned study product starting the evening of enrollment day and to continue for five consecutive days. For missed doses study participants will be instructed not to double up on doses and to take the prescribed dose at the next scheduled administration time. Study product should be stored away from children so to avoid unintended administration by unauthorized study participants.

Study participants who will be undergoing blood sampling procedures will not be randomized or receive placebo.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Active ingredients for the zinc/EGCG/ascorbic acid blend will be procured from a U.S. based supplements supplier (www.bulksupplements.com; FDA registration number: 17938017996) at the following amounts factoring in a 20% waste tolerance and available package size.

1. Zinc citrate – 200g
2. Green tea extract (≥50% EGCG) – 500g
3. Ascorbic acid – 200g

Placebo ingredients will be procured from the MUHC investigation pharmacy services at the following amounts factoring in a 20% waste tolerance and available package size.

1. Microcrystalline cellulose – 1kg

Compounded capsules of both the study supplement product and placebo will be assessed for weight variability with a 10% variance allowed. Capsules will be prepared in small batches throughout the study period based on the anticipated weekly accrual rate of enrollment. Each batch will be assigned a unique lot number, their own compound log, and up to a 180 day expiration date. Storage will occur in the investigational drug pharmacy where compounded capsules will be kept in a standard amber colored prescription bottle with a desiccant placed within the bottle to absorb any ambient moisture. Temperature monitoring will occur daily by the investigation drug pharmacist with a target range of 20°C – 25°C per United States Pharmacopoeia (USP) and the supplement manufacture's recommendations. The investigational drug pharmacist or designated pharmacist will receive a study prescription from an authorized prescriber following patient enrollment for processing, which includes assignment of randomization, filling of prescription with required documentation and labeling, and coordination with the ED study staff for delivery to the patient in the ED. Study patients will be discharged from the ED with their study drug before returning home later that day. Unused study drug returned by participants will be received by the investigational drug pharmacy for proper documentation, storage, and eventual destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study products will be prepared using University of Missouri Health Care (MUHC) pharmacy compounding resources using traditional practices of geometric dilution and capsulation. Compounding and dispensing of study supplement and placebo will be in compliance with Missouri Board of Pharmacy regulation 20 CSR 2220.2.400 Compounding Standards of Practice. White, opaque size 0 gelatin capsules will be used to prepare both study supplement and placebo, and will be dispensed into amber prescription bottles with tamper resistant tops for patient delivery. Labeling of study product will be in such a way to maintain blinding, but will include all information as required by state and federal regulations including: 1) The date the prescription was filled; 2) A prescription number or other unique identifier; 3) The patient's name; 4) The prescriber's directions for use; 5) The prescriber's name; 6) The pharmacy/institution's name, address, and contact information; 7) blinded name of study drug dispensed. The Federal Investigational Drug Caution Statement—"CAUTION: Drug limited by Federal (United States) Law to investigational use only."—will be applied to the study drug products.

6.2.3 PRODUCT STORAGE AND STABILITY

Storage requirements for study products will be in accordance with the individual component manufacture recommendations and USP. This includes keeping compounded capsules in a dry and cool environment with a target temperature of 20°C – 25°C. To minimize moisture a desiccant will be placed in the bulk bottles containing prepared study supplement and placebo capsules, respectively. An expiration date of up to 180 days will be given to compounded capsules to limit any unknown loss of potency that may occur with a long-dated expiration. This dating is in accordance with United States Pharmacopeia (USP) General Chapter 795 guidance for non-sterile compounding.

6.2.4 PREPARATION

Study capsules for combination supplementation will be prepared by compounding each of the three individual components using a porcelain mortar and pestle and method of geometric dilution. The mixed fine powder will be used to fill white colored size 0 gelatin capsules using a capsule machine with a 100 capsule capacity. A 10% variability tolerance will be permitted for under/over filling of each capsule with a target weight of 438mg per capsule. Placebo capsules will be prepared in a similar fashion using microcrystalline cellulose with identical capsules and a fill weight target of 300mg ± 10%. All compounding will occur on site at MUHC in a dedicated non-sterile compounding room located in the inpatient pharmacy.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will be performed using an online generator (*http://www.randomization.com*) that assigns study subjects to a single treatment arm using randomly permuted blocks. The investigational drug pharmacist will conduct maintenance of trial randomization codes and appropriate blinding. Double blinding will be used to limit recall and observer bias given the subjectivity of the primary outcome. Opaque, white colored capsules of the same size will be used to prepare both study supplement and placebo capsules to conceal treatment assignment. Serious adverse events requiring medical care that are suspected to be caused from the study drug or an unintentional ingestion of study drug by non-study participants will initiate un-blinding procedures. This will include contacting research pharmacy personnel or their designee by medical staff treating the adverse event. Research pharmacy personnel are available during normal business hours, however, their designee (other MUHC inpatient pharmacists) will be available 24 hours a day, seven days a week. Treating medical staff will be immediately informed of the study subject's randomization assignment by the research pharmacist or their designee for purposes of emergent medical care; recording of the unblinding will be performed by the research pharmacist and notification will be sent to the primary investigator and Independent Safety Monitor within 24 hours. Documentation of an unblinding event will include: identification of participant unblinded, reason for unblinding, date and time of unblinding, how unblinding information was obtained, and which research team member(s) have been unblinded. Study participants will be removed from the study if they experience an adverse event that requires medical care due to complications from worsening respiratory viral illness or study drug. Patients not removed will be contacted daily via telephone visits for seven consecutive days by MUHC emergency department research staff starting the day after enrollment day for collection of primary and secondary outcome data elements. MUHC emergency department research staff are trained technicians autonomous of study teams for purposes of clinical trial and facilitate independent data collection for study endpoints. Following the seven days of follow-up patients will be dismissed from study participation and will be instructed to follow-up with their primary care provider for any future medical needs.

6.4 STUDY INTERVENTION COMPLIANCE

Compliance of study intervention will be assessed by MUHC emergency department research staff via daily telephone visits. Occurrences of non-compliance will be patient-reported and include number of missed doses for any given day during the on-treatment follow-up period.

6.5 CONCOMITANT THERAPY

Patients enrolled will be instructed to discontinue any current OTC products that contain any of the components of the study drug to mitigate confounding of treatment effect. Common cough and cold products that do not share ingredients with study drug will be allowed, and daily utilization will be quantified as name and number of products used and doses of each taken daily using a patient 'sick' diary. This strategy will allow standard-of-care treatment via patient directed symptom management using traditional OTC cough and cold medicines, while minimizing bias in evaluation of study outcomes.

6.5.1 RESCUE MEDICINE

The study site and sponsor will not supply OTC cough and cold rescue medication. Obtainment of this type of therapy will be at the discretion of the study participants with the restriction that no product should include any amount of the study supplement individual components of zinc, green tea, or ascorbic acid (vitamin C).

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study supplement or placebo 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).

Adverse events necessitating discontinuation from the study including removing patients from follow-up telephone visits for any remaining outcome related data collection include any event that would lead to a patient requiring hospitalization. This includes hospitalization related to a suspected adverse event from study drug resulting in unblinding procedures or for worsening respiratory status. Patient self-discontinuation of study intervention due to intolerance affecting future compliance will allow patients to remain in the study to complete any remaining telephone visits for primary and secondary endpoint data collection. Efforts to promote compliance including reinforcing patients to administer study product two hours following a meal will be employed before discontinuing patients from study intervention, but patient refusal to continue with treatment will be considered a dropout with an attempt to collect remaining telephone visits for completeness of endpoint related data capture.

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

- Date of study discontinuation
- Reason for discontinuation
- Number of study days completed prior to discontinuation of treatment/study withdrawal
- Total number of patient-reported doses taken of study drug prior to discontinuation of treatment/study withdrawal

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:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE) necessitating hospitalization
- Disease progression which requires hospitalization
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may also be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for seven consecutive scheduled telephone visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return a missed telephone contact for a required study visit:

- The site will attempt to contact the participant to reschedule the missed visit within the same business day as the originally scheduled appointment, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone call attempts within the same business day). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patients presenting to MUHC emergency department for cold and flu-like symptoms during the study period will be assessed for eligibility by the admitting physician based on protocol inclusion and

exclusion criteria as previously detailed. Standard evaluation and collection of patient overall health status including past medical history, vital signs, physical exam, necessary imaging, and laboratory assessment will be completed as part of routine care associated with the emergency department visit. Patients enrolled into the study will be randomized and provided study drug the same day of their emergency department visit such that patients will not discharge from the emergency department until they have received their study drug and corresponding instructions for study participation. Testing results including COVID-19 status or positive influenza will be communicated via telephone contact to study patients as part of routine care follow-up and in accordance with MUHC emergency department procedures. Patients meeting exclusion criteria following results of study related testing information will be instructed to discontinue study intervention and follow-up with their primary care provider or other non-study related healthcare provider for appropriate management.

Upon receiving study drug and following discharge from the emergency department study subjects will begin self-administering study product as outlined in section 6.1.2 of this protocol the evening of the day of enrollment. Research staff from the MUHC emergency department will begin contacting patients the following day and daily thereafter for a total of seven consecutive days as described in section 1.3 of this protocol. The following data elements are to be collected each day via telephone visits for the efficacy endpoints:

Primary efficacy endpoints:

Symptom	Severity Score 0 – absent, 1- mild, 2- moderately sever, 3 – very severe
nasal drainage	
nasal congestion	
sneezing	
scratchy throat	
sore throat	
cough	
headache	
hoarseness	
muscle ache	
shivering or feverish	
tiredness	
difficulty in concentration	
Total Severity Score (max: 36 points)	

Recovery from cold and flu-like illness defined as daily total symptom severity score of 0 or 1	Yes or No
day 2	
day 3	
day 4	
day 5	
day 6	

day 7	
day 8	

Secondary efficacy endpoints:

Morbidity Event	Yes or No
missed days from work or school number of days	
hospitalization or physician office visit(s) for respiratory viral illness related complications	

Additional data elements to be collected with each daily telephone visit that do not pertain to the primary and secondary endpoints, but remain clinically relevant include patient reported use of any OTC cough and cold medicine(s) for which MUHC emergency department research staff will record the number of the different products used, each product(s) name, and the number of doses of each product taken by the patient. Patients will be encouraged to record their OTC medication use using a 'sick' diary, but this will not be a formal requirement of the protocol. Study subjects will also be asked about how many doses were missed in the preceding 24 hours during the daily telephone visits conducted by MUHC emergency department research staff. For patients that withdraw early from the study the following information will be collected at their last visit if possible:

- Date of study discontinuation
- Reason for discontinuation
- Number of study days completed prior to discontinuation of treatment/study withdrawal
- Total number of patient-reported doses taken of study drug prior to discontinuation of treatment/study withdrawal

Relevant patient demographic information including: age, sex, ethnicity, history of asthma, COPD, diabetes, COVID-19 status, hospitalization for respiratory condition within the past year will be obtained using existing health record data.

Study subjects participating in blood sampling procedures will not be contacted daily for collection of efficacy assessments.

8.2 SAFETY AND OTHER ASSESSMENTS

Patients presenting to MUHC emergency department for cold and flu-like symptoms during the study period will be assessed for eligibility by the admitting physician based on protocol inclusion and exclusion criteria as previously detailed. Standard evaluation and collection of patient overall health status including past medical history, vital signs, physical exam, necessary imaging, and laboratory assessment will be completed as part of routine care associated with the emergency department visit. Patients enrolled into the study will be randomized and provided study drug the same day of their emergency department visit such that patients will not discharge from the emergency department until they have received their study drug and corresponding instructions for study participation. Testing results including COVID-19 status or positive influenza will be communicated via telephone contact to study patients as part of routine care follow-up and in accordance with MUHC emergency department

procedures. Patients meeting exclusion criteria following results of study related testing information will be instructed to discontinue study intervention and follow-up with their primary care provider or other non-study related healthcare provider for appropriate management.

Upon receiving study drug and following discharge from the emergency department study subjects will begin self-administering study product as outlined in section 6.1.2 of this protocol the evening of the day of enrollment. Research staff from the MUHC emergency department will begin contacting patients the following day and daily thereafter for a total of seven consecutive days as described in section 1.3 of this protocol. The following data elements are to be collected each day via telephone visits for the safety endpoints:

Safety endpoints:

Adverse Effect	Yes or No
nausea	
vomiting	
indigestion	
worsening of shortness of breath or difficulty breathing	
allergic reaction skin rash hives swelling of lips or tongue	
hospitalized or physician visit for study drug related adverse effect	

Additional data elements to be collected with each daily telephone visit that do not pertain to the primary and secondary endpoints, but remain clinically relevant include patient reported use of any OTC cough and cold medicine(s) for which MUHC emergency department research staff will record the number of the different products used, each product(s) name, and the number of doses of each product taken by the patient. Patients will be encouraged to record their OTC medication use using a 'sick' diary, but this will not be a formal requirement of the protocol. Study subjects will also be asked about how many doses were missed in the preceding 24 hours during the daily telephone visits conducted MUHC emergency department research staff. For patients that withdraw early from the study the following information will be collected at their last visit if possible:

- Date of study discontinuation
- Reason for discontinuation
- Number of study days completed prior to discontinuation of treatment/study withdrawal
- Total number of patient-reported doses taken of study drug prior to discontinuation of treatment/study withdrawal

Relevant patient demographic information including: age, sex, ethnicity, history of asthma, COPD, diabetes, COVID-19 status, hospitalization for respiratory condition within the past year will be obtained using existing health record data.

Study subjects participating in blood sampling procedures will not be contacted daily for collection of pre-defined safety assessments.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Independent Safety Monitor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21CFR312.32).

8.3.2.1 EXPECTEDNESS

The principle investigator along with co-investigators 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.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- MILD: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- MODERATE: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- SEVERE: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

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: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- POSSIBLY RELATED: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- NOT RELATED: The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

8.3.3.3 EXPECTEDNESS

The principle investigator along with co-investigators 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.

- UNEXPECTED - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- EXPECTED - event is known to be associated with the intervention or condition under study.

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 during study visits 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, 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.

Study research technicians will record all reportable events via daily telephone visits with start dates occurring sometime near 24 hours after informed consent is obtained and continue until 2 days (for non-serious AEs and SAEs) after the last planned day of study drug administration (total of 7 days). At each study visit, study research technicians will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Solicited events will include patient self-reported:

- Nausea
- Vomiting
- Indigestion
- Worsening of shortness of breath or difficulty breathing
- Allergic reaction
    - skin rash
    - hives
    - swelling of lips or tongue
- Hospitalized or physician visit for study drug related adverse effect

Unsolicited events will include any patient self-reported adverse event that is provided without prompting by the research technician and that is not related/similar to any of the solicited events being collected.

8.3.5 ADVERSE EVENT REPORTING

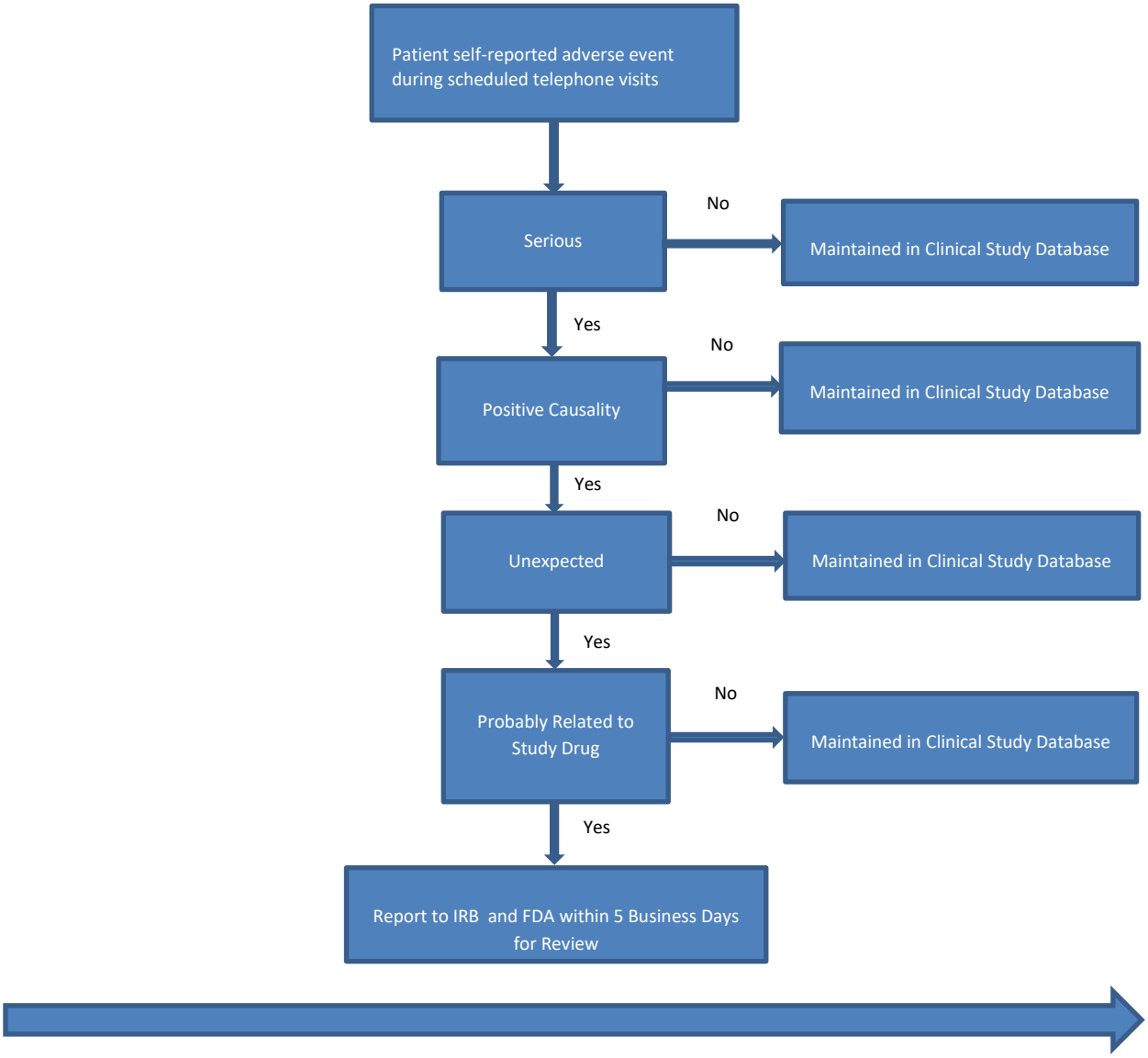
Formal data safety monitoring will occur every two weeks by an Independent Safety Monitor. A review of events necessitating unblinding of study subjects, overall rate of solicited and unsolicited adverse events, as well as the rate of patient reported self-dropout due to intolerance will be continuously monitored throughout the study period. If the overall dropout rate exceeds 10% at any time or a study subject experiences a serious adverse event the Investigational Review Board (IRB) will be notified within five business days for review. The study period will be terminated early if the IRB, Independent

Safety Monitor, or study investigators determine that the study jeopardizes patient safety beyond an expected risk level at any time.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study research team including technicians and co-investigators will immediately report to the primary investigator and Independent Safety Monitor 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 (a physician research team member must determine probability of adverse event occurring due to study drug). Study endpoints that are serious adverse events (e.g. hospitalization for either a suspected study drug related adverse event or worsening respiratory status from viral infection) 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., hospitalization from anaphylaxis). In that case, members of the research team or other involved party such as the investigational drug pharmacist in cases of unblinding must report the event to the primary investigator and Independent Safety Monitor within 24 hours. The primary investigator must report any unexpected serious adverse event to the IRB within 5 business days. 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 primary investigator 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 5 business days after the primary investigator's receipt of the information. In addition, primary investigator 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 5 business days after the primary investigator determines that the information qualifies for reporting. See below flow chart for serious adverse event reporting scheme:


Patient self-reported adverse event during scheduled telephone visits
Serious
No
Maintained in Clinical Study Database
Yes
Positive Causality
No
Maintained in Clinical Study Database
Yes
Unexpected
No
Maintained in Clinical Study Database
Yes
Probably Related to Study Drug
No
Maintained in Clinical Study Database
Yes
Report to IRB and FDA within 5 Business Days for Review
Follow-Up Days 1-7
(Beginning Day After Study Enrollment)

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Patients will not be informed of adverse events apart from those self-reported by them during secondary endpoint data collection. Incidental findings from study enrollment will be communicated via telephone contact to study patients as part of routine care follow-up and in accordance with MUHC emergency department procedures.

8.3.8 EVENTS OF SPECIAL INTEREST

A separate study is planned that will collect blood samples in 10 patients to assess serum concentrations of zinc and EGCG, and a complete metabolic panel (CMP) following five days of taking study drug. Patients will be selected using the same criteria as those enrolled in the placebo-controlled trial, but will not be randomized to blinded treatment given the logistical requirements necessitating accurate blood sampling. These patients will also not be a part of primary and secondary endpoint collection via daily telephone visits. The purpose of this study is to simply describe peak serum levels of zinc and EGCG following multiple dosing of the study drug, as well as to assess the rate of transaminitis if any is to occur. Occurrences of transaminitis for which the alanine transaminase (ALT) is >3x the ULN *AND* the total bilirubin is >2xULN will prompt reporting to the FDA within 5 business days. A separate consent form will be used for this aspect of the research.

8.3.9 REPORTING OF PREGNANCY

Pregnant patients or those planning to become pregnant will be excluded from study participation. If a patient enrolled becomes pregnant anytime during the follow-up period then the study drug will be stopped and the patient will be discontinued from the study. The IRB will not be notified unless the patient meets reporting criteria from experiencing a serious adverse event.

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 possibly related to participation in the research ("possibly related" means there is a reasonable possibility 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 to the lead principal investigator (PI). 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 within 5 business days and to the primary investigator and Independent Safety Monitor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and primary investigator within 5 businesbusiness 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 48 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Patients will not be informed of unanticipated problems apart from those self-reported by them during primary and secondary endpoint data collection, or those necessitating premature termination or suspension of the study as a whole.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

1. Combination supplementation with zinc, green tea extract, and ascorbic acid is associated with a decrease in duration and severity of cold and flu-like symptoms following five days of treatment as compared to placebo (superiority analysis). Analysis will be conducted following seven days of follow-up.

- Secondary Efficacy Endpoint(s):

1. Rates of adverse events including, nausea, vomiting, indigestion, worsening of shortness of breath or difficulty breathing, allergic reaction (skin rash, hives, swelling of lips or tongue), and hospitalized or physician visit for study drug related adverse effect will not occur more frequently with combination supplementation with zinc, green tea extract, and ascorbic acid as compared to placebo (superiority analysis). Analysis will be conducted following seven days of follow-up.
2. Rates of patient-reported days missed from work or school and hospitalization or physician office visit(s) for respiratory viral illness related complications will occur less frequently with combination supplementation with zinc, green tea extract, and ascorbic acid as compared to placebo (superiority analysis). Analysis will be conducted following seven days of follow-up.

9.2 SAMPLE SIZE DETERMINATION

The target number of subjects to be enrolled during the study period occurring May 2022 – June 2023 is 100 (50 patients randomized to placebo and 50 to the supplementation group). This target is derived from a similarly conducted study evaluating zinc supplementation (without green tea extract) in a comparable adult population as identified with the current proposal.[34] Based on an assumption that 60% of patients taking study drug and 30% in the placebo group would recover from cold and flu-like symptoms after five days of treatment a total of 84 patients would be sufficient to reach 80% power with a two tailed p value <0.05 to detect differences between groups. The power calculation was

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.45 * 0.55 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.3 * 0.7 + (\frac{0.6 * 0.4}{1})} \right\}^2 / 0.3^2$$

$$N_1 = 42$$

$$N_2 = K * N_1 = 42$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

performed using an online tool located at https://clincalc.com/stats/samplesize.aspx with the following calculations performed:

The anticipated dropout rate is 5% based on a large randomized control study evaluating safety of EGCG following 12 months of treatment using a similar daily dosage as the current proposal.[24] No interim analysis is planned; power calculation is for primary endpoint only.
The primary outcome will be compared using the Chi-square test. Secondary outcomes will be assessed using the Chi-square test for categorical data and student's t-test for continuous data. An exploratory analysis comparing the primary outcome among COVID-19 only patients will also be conducted. All inferential testing will be based on intention-to-treat.

9.3 POPULATIONS FOR ANALYSES

All endpoints will be assessed using intention-to-treat analysis. This will include all randomized participants.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics for continues data will be expressed at means with standard deviations and categorical data will be expressed as percentage of total cohort. Inferential testing will use two-tailed p value <0.05 with 95% confidence intervals to determine statistical significance.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint will be determined from observing the proportion of patients (expressed as percentage) recovered from cold and flu-like symptoms (defined as scoring 0 or 1 daily total symptom severity score) following seven days of follow-up. Recovery from cold and flu-like symptoms will be categorically assessed as a single endpoint. The difference in recovery rates between study drug and placebo will be compared using Chi-squared test and be expressed with 95% confidence intervals. Analysis will be performed based on intention-to-treat. Missing data will be handled by last observation carried forward based on most recent self-reported total daily symptom severity score.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints are independent of findings from the primary endpoint.

Rates of adverse events will be determined as a percentage of those subjects self-reporting an event compared to the total cohort following seven days of follow-up. Adverse events will be categorically expressed as a single endpoint. Difference in adverse events will be compared using Chi-squared test with incidence rates expressed as percentages. Analysis will be performed based on intention-to-treat. Missing data will be handled by last observation carried forward based on most recent self-reported adverse event (or lack thereof).

Rates of missed days of work or school will be determined as a percentage of those subjects self-reporting a missed day compared to the total cohort following seven days of follow-up. Missed days will be both categorically expressed as a single endpoint with incidence rates expressed as percentages as well as mean days missed with standard deviation. Difference in missed days will be compared using Chi-squared test for categorically expressed missed days (occurrence of any missed day(s) during study follow-up) and student's t-test for mean days missed. Analysis will be performed based on intention-to-treat. Missing data will be handled by last observation carried forward based on most recent self-reported missed day (or lack thereof).
Rates of seeking medical care including physician office visits or hospitalization for worsening respiratory illness will be determined as a percentage of those subjects self-reporting these events compared to the total cohort following seven days of follow-up. A physician office visit or hospitalization for worsening respiratory illness will be categorically expressed as a single endpoint with incidence rates expressed as percentages. Difference in need to seek medical care will be compared using Chi-squared tests. Analysis will be performed based on intention-to-treat. Missing data will be handled by last observation carried forward based on most recent self-reported medical visit (or lack thereof).

9.4.4 SAFETY ANALYSES

Rates of adverse events including, nausea, vomiting, indigestion, worsening of shortness of breath or difficulty breathing, allergic reaction (skin rash, hives, swelling of lips or tongue), and hospitalized or physician visit will be included in secondary analysis as out outlined in **Section 9.4.3**. Unsolicited adverse events recorded will be categorized as "other adverse events" and will be described as a incidence rate expressed as a percentage. Each adverse event recorded will be only counted once for any given study subject during the study follow-up period. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes will be used to code adverse events where appropriate. Severity of adverse events will be classified as follows:

- MILD: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- MODERATE: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- SEVERE: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Expectedness of adverse events will be determined as follows:

- UNEXPECTED - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- EXPECTED - event is known to be associated with the intervention or condition under study.

Relatedness of adverse events will be determined as follows:

- DEFINITELY RELATED: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- POSSIBLY RELATED: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- NOT RELATED: The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Dates of adverse events self-reported by study participants will be recorded, and any adverse event leading to premature discontinuation from the study including serious treatment-emergent AEs will be listed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics planned to be collected include the following:

- age
- sex
- height
- weight
- ethnicity
- history of asthma
- history of chronic obstructive pulmonary disease (COPD)
- history of diabetes
- COVID-19 status
- history of hospitalization for respiratory condition within the past year

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Sub-group analysis based on patient demographic variables (e.g. age, sex, race/ethnicity) will not be performed.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Study subject data will be tabulated by measure and time point through the study follow-up period.

9.4.9 EXPLORATORY ANALYSES

The impact of combination supplementation against placebo on symptom duration and severity in the COVID-19 positive subgroup of enrolled patients will be assessed as an exploratory endpoint. This outcome will be determined from observing the proportion of COVID-19 positive patients (expressed as percentage) recovered from cold and flu-like symptoms (defined as scoring 0 or 1 daily total symptom severity score) following seven days of follow-up. Recovery from cold and flu-like symptoms will be categorically assessed as a single endpoint. The difference in recovery rates between study drug and placebo will be compared using Chi-squared test and be expressed with 95% confidence intervals. Analysis will be performed based on intention-to-treat. Missing data will be handled by last observation carried forward based on most recent self-reported total daily symptom severity score.

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

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are provided separately from this protocol:

Consent for randomized control trial
Consent for separate blood sample study

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

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. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will 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 in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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. Non-English-speaking patients will be offered language interpreting services for purposes of consenting. Patients not able to make sound decisions for themselves will not be approached for consent and study enrollment.

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, investigators, 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 Independent Safety Monitor 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
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the 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 and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition 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 primary investigator.

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

The study monitor, other authorized representatives of the primary investigator, representatives of the Institutional Review Board (IRB), and 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 at each clinical site 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 and Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at University of Missouri Health Care. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Given the ubiquitous nature of cold and flu-like illness, including COVID-19, deidentified information including patient demographic data such as age, ethnicity, sex, etc. is not expected to make any individual or group of individuals identifiable. The key for identifying patients with their unique study number will be kept with the Investigational Drug Service (IDS) pharmacist for the duration of the study period, and it will be stored under lock and key in the IDS pharmacy or password protected in a dedicated IDS database folder located at University of Missouri Health Care for digital storage. The study data entry and study management systems used by clinical sites and by University of Missouri Health Care research staff will be secured and password protected. Sharing unidentified data will occur as necessary amongst research team members as well as the study monitor for such reasons as to review adverse events including assessment of severity, expectedness, and relatedness. At the end of the study, all study databases will be de-identified and archived at University of Missouri Health Care.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Specimens collected as part of this study will not be kept for future studies. Specimens obtained will be discarded in accordance with each laboratory's policy and procedures upon completion of their respective analyses. Any specimens not destroyed at time of study end will be discarded in accordance to the respective laboratory's policy and procedures.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Syed Naqvi, MD Associate Professor of Clinical Medicine Division Director, Hospital Medicine Associate Chief Medical Officer, MU Health Care	Taylor Nelson, MD Medical Director, General Infectious Disease Clinic Director of Social Media Outreach Assistant Professor of Clinical Medicine
University of Missouri. Health Care	University of Missouri. Health Care
1 Hospital Dr, Columbia, MO 65212	1 Hospital Dr, Columbia, MO 65212
573 884 9066	573 882 8788
naqvis@health.missouri.edu	nelsontb@health.missouri.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an Independent Safety Monitor (ISM) composed of an individual with expertise in Infectious Disease. Members of the ISM 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 ISM will meet regularly at enrollment intervals of 25%, 50%, 75%, and 100% of target to assess safety data on each arm of the study. The ISM will provide its input to the primary investigator and Institutional Review Board.

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 Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The Independent Safety Monitor (ISM) will conduct clinical monitoring, on-site, at enrollment intervals of 25%, 50%, 75%, and 100% of target throughout the study period. Safety data including adverse events, events necessitating unblinding, and the ongoing dropout rate will be comprehensively reviewed. Reports of data monitored will be provided to the primary investigator and Institutional Review Board as necessary. Serious adverse events or events leading to unblinding procedures will be reported to the ISM and primary investigator within 24 hours for review.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. Quality management for specimens collected will be in accordance to each laboratory's established quality assurance procedures. Tracking logs and digital communication records will be used to ensure reception and completed analysis of specimens collected.

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.

The study investigators will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, 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 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.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source documents will include hardcopy case report forms that will include baseline characteristic information as described in **Section 9.4.5** of this protocol, data elements relevant to primary and secondary endpoints as described in **Sections 8.1 and 8.2** of this protocol, unsolicited adverse events, date of serious adverse event occurrence, severity, estimated expectedness, and relatedness of adverse events, and information pertinent to patients discontinued from study participation as outline in **Section 7.3** of this protocol. A separate case report form will be used to collect laboratory data as described in **Section 8.3.8** of this protocol.

Hardcopies of the study visit case report forms will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. Study team members will transmit study subject hardcopy visit worksheets into corresponding electronic case report forms within one week of completing the hard copy worksheet on an ongoing bases throughout the study period. Electronic case report forms will be kept centrally in a secured manner including password protection at University of Missouri Health Care and be used to capture the ongoing dropout rate, serious adverse events, and events leading to unblinding; these reports will be used by the Independent Safety Monitor for review. Findings necessitating reporting to the appropriate regulatory bodies such as the IRB will be generated from this data collection procedure. Serious adverse events or events necessitating unblinding will be recorded using hardcopy case report forms upon initial collection/identification. Although the electronic version of the data is to be captured within one week of completing hardcopy case report forms, direct communication via telephone and/or email to the primary investigator and the Independent Safety Monitor upon discovering one of these events will occur with 24 hours as described in this protocol.

Laboratory data associated with study procedures as described in **Section 8.3.8** will be kept in accordance with each laboratory's local practices and policies. These data will not be retained for future use once the study has completed and thus retention of records will be in accordance with each laboratory's local practices and policies. Transmission of data from the respective laboratories will occur electronically using the University of Missouri Health Care electronic health record system where feasible, otherwise information will be collected securely through encrypted electronic communications on an ongoing basis throughout the study period.

Clinical data and clinical laboratory data obtained as part of routine care captured during study enrollment will be entered into University of Missouri Health Care electronic health record system, *Cerner Millennium PowerChart*, provided by Cerner Corp. This platform is not certified as it relates to 21 CFR Part 11 as records kept for patient care purposes are not applicable. However, these records are maintained in accordance to other state and federal requirements including HIPPA Privacy and Security Rules. This platform is certified for the purposes of the Meaningful Use incentive program.

10.1.9.2 STUDY RECORDS RETENTION

It is the investigators responsibility to maintain adequate documentation of research procedures/process/data in printed form or electronically. Retention of all study related data will be kept for at least seven years after conclusion of the study in accordance with local policies and regulations set forth by the Investigational Review Board.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization 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 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the primary investigator and Institutional Review Board. 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

Publication will be decided amongst the study investigative team based on contribution to study design and development, execution, and role in securing funding for study related costs.

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and 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 peer-reviewed journals.

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 managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with University of Missouri Health Care has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

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
CRF	Case Report Form
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
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 Harmonization
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
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.2	November 24, 2021	Changed study dates	Delay in funding; planned award release in December 2021
1.3	April 12, 2022	Changed study dates Capsules used will be white and opaque	Delay in funding; planned award release in April 2022 Changing capsule manufacture (for entire study) due to supply issues with original capsule
1.4	August 11, 2022	Changed dosing instructions and the mg weight of each study component per capsule. Zinc citrate product corrected to be 32% elemental zinc by weight	Changed dosing instructions to reflect three (3) capsules taken twice daily as capsule fill capability was limited; importantly the total daily exposure of each study component has NOT changed
1.4	August 11, 2022	Added legend at bottom of chart Updated activities to include daily telephone visits and removed biochemical pregnancy test	IRB review feedback to include definition of superscript letter(s) and to indicate which activities are a part of routine care Include telephone visits as part of the schedule of activities table to better capture full study procedures in the table; removed pregnancy test as this status will be obtained verbally
1.4	August 11, 2022	Updated to account for new COVID-19 treatments	IRB review feedback to address context of newer COVID-19 treatments as it relates to this study protocol
1.4	August 11, 2022	Updated to include use of advertisements	Using advertisements to increase awareness of study activities
1.4	August 11, 2022	Updated to clarify that study subjects undergoing blood sampling procedures will not be randomized or assigned to placebo	IRB review feedback requested clarification
1.4	August 11, 2022	Updated to clarify that study subject undergoing blood	IRB review feedback requested clarification

		sampling procedures will not be contacted via daily telephone visits for collection of efficacy and pre-defined safety assessments	
1.4	August 11, 2022	Updated to include medical monitor	Medical monitor identified and added to protocol
1.4	August 11, 2022	Updated history of changes made to IRB approved versions of the protocol	IRB feedback requested this update
1.4	August 11, 2022	Added legend at bottom of chart Updated activities to include daily telephone visits and removed biochemical pregnancy test	IRB review feedback to include definition of superscript letter(s) and to indicate which activities are a part of routine care Include telephone visits as part of the schedule of activities table to better capture full study procedures in the table; removed pregnancy test as this status will be obtained verbally
1.5	November 14, 2022	Changed inclusion criterion from ≤ 36 hours to < 72 hours	Current symptom duration criterion is demonstrating to be too restrictive and impairing enrollment. Increase time to < 72 hours to help with enrollment efforts.

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Addendum A

BULK SUPPLEMENTS.com
CLEAN & PURE BULK SUPPLEMENTS

Finished Goods Specification Sheet

Product Name	Zinc Citrate	
Item Code	FPZIN-01	
Item	**Specifications**	**Method**
Appearance	Fine white powder	Organoleptic
Odor	Slightly citrusy	Organoleptic
Identification	NLT 95 %	FTIR
Assay (as Zinc, as-is)	NLT 31.3 %	Titration
Assay (as Zinc Citrate 3H2O)	NLT 99.0 %	
Heavy Metals		
Arsenic	NMT 1.0 ppm	ICP-MS
Cadmium	NMT 5.0 ppm	ICP-MS
Lead	NMT 10.0 ppm	ICP-MS
Mercury	NMT 0.5 ppm	ICP-MS
Microbial Results		
Total Plate Count	NMT 1,000 cfu/g	Petrifilm
Yeast and Mold	NMT 100 cfu/g	Petrifilm
Total Coliform	NMT 10 cfu/g	Petrifilm
Enterobacteriaceae	ABSENT	Petrifilm
E. coli	ABSENT	Petrifilm

Prepared by: Amal Ray Date: 6/19/2020

Qc reviewed and approved by: [signature] Date: 06-19-2020

Hard Eight Nutrition, LLC

7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222

SAFETY DATA SHEET

Section 1: Identification

Product Name: Zinc Citrate
Chemical Name/Synonyms: Zinc citratetribasicdihydrate Citric acidzinc salt
Company: Hard Eight Nutrition, LLC Dba BulkSupplements.com
7511 Eastgate Road, Henderson, NV 89011 USA Telephone: 702-293-0222

In emergency call 911.
For information about this SDS, use this department contact phone#: 702-293-0222

Section 2: Hazard(s) Identification

Classification of the substance or mixture
Not a hazardous substance or mixture.
GHS Label elements, including precautionary statements
Not a hazardous substance or mixture.
Hazards not otherwise classified (HNOC) or not covered by GHS - none

Section 3: Composition/ Information on Ingredients

Chemical Name	Chemical formula	CAS#	Conc.
Zinc citratetribasicdihydrate Citric acidzinc salt	$C_{12}H_{10}O_{14}Zn_3.2H_2O$	5990-32-9	≤100%

Section 4: First-Aid Measures

After skin contact: Wash off with soap and plenty of water. Consult a physician.
After eye contact: Rinse with plenty of water for at least 15 minutes and consult a physician.
After inhalation: Move to fresh air. If not breathing, give artificial respiration. Consult a physician.
After swallowing: Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

Section 5: Fire-Fighting Measures

Suitable extinguishing agents: Water spray, alcohol-resistant foam, dry chemical, or carbon dioxide.
Special Remarks on Explosion Hazards: No data available
Special protective equipment for firefighters: Use self-contained breathing apparatus for firefighting if necessary.

Section 6: Accidental Release Measures

Personal precautions: Use personal protective equipment. Avoid dust formation. Ensure adequate ventilation.
Measures for environmental protection: Do not let product enter drains
Measures for cleaning/collecting: Sweep or shovel into a closed container for disposal.

Section 7: Handling and Storage

Handling: Avoid contact with skin and eyes. Avoid formation of dust. Provide exhaust ventilation at places where dust is formed.
Storage: Keep container closed in a dry, well ventilated place.

Section 8: Exposure Controls/Personal Protection

Engineering Controls: Handle in accordance with good industrial hygiene and safety practice. Wash hands frequently.
General protective and hygienic measures: Follow good industrial hygiene.
Breathing equipment: Wear a type P95 or type P1 respirator.
Protection of hands: Wear suitable gloves prior to handling.
Eye protection: Wear suitable eye protection.

Section 9: Physical and Chemical Properties

Form: Solid
Color: White
Odor: Odorless
Odor threshold: No data available
pH: No data available
Melting point/melting range: No data available
Boiling point/boiling range: No data available
Flash point: No data available
Evaporation rate: No data available
Flammability: No data available
Upper/lower flammability or explosive limits: No data available
Auto ignition temperature: No data available
Danger of explosion: No data available
Vapor pressure: No data available
Vapor density: No data available
Relative density: No data available
Solubility in/Miscibility with water: No data available

Section 10: Stability and Reactivity

Stability: Stable under recommended storage conditions
Materials to avoid: Avoid moisture.
Incompatibility: Strong oxidizers.

Section 11: Toxicological Information

Skin: No data available
Eyes: No data available
Inhalation: No data available
Ingestion: No data available

Section 12: Ecological Information (non-mandatory)

Ecotoxicity: Very toxic to aquatic life with long lasting effects.
BOD5 and COD: No data available
Products of Biodegradation: No data available
Toxicity of the Products of Biodegradation: No data available
Special Remarks on the Products of Biodegradation: No data available

Section 13: Disposal Considerations (non-mandatory)

Product

Offer surplus and non-recyclable solutions to a licensed disposal company

Contaminated packaging

Dispose of as unused product.

Section 14: Transport Information (non-mandatory)

Not dangerous goods

Section 15: Regulatory Information (non-mandatory)

SARA 302 Components

No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components

The following components are subject to reporting levels established by SARA Title III, Section 313

SARA 311/312 Hazards

No SARA hazards

Section 16: Other Information

The information provided in this safety data sheet is the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

SDS date of preparation/update: 7/23/2020

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CLEAN & PURE BULK SUPPLEMENTS
7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222 | Email: Cs@Bulksupplements.com

Certificate of Analysis

Product Name	Zinc Citrate		
Bulk Supplements Lot #	2003903		
Manufacturer Date	03-20-2020		
Expiration Date	03-30-2022		
Item	**Specifications**	**Method**	**Results**
Description	White powder	Organoleptic	Conforms
Identification	NLT 95%	FT-IR	99.7 %
Assay (as-is)	NLT 97.0 %	Titration	98.7 %
	NLT 31.3 % Zinc	Titration	31.7 % Zn
Loss on drying	NMT 1.0 %	Moisture Balance	0.8 %
Heavy Metals			
Arsenic	NMT 3.0 ppm	ICP-MS	< 3 ppm
Cadmium	NMT 5.0 ppm	ICP-MS	< 5 ppm
Lead	NMT 10 ppm	ICP-MS	< 10 ppm
Microbiological			
Total Plate Count	NMT 10,000 cfu/g	Petrifilm	< 10 cfu/g
Yeast and Mold	NMT 1,000 cfu/g	Petrifilm	< 10 cfu/g
Total coliform	NMT 10 cfu/g	Petrifilm	< 10 cfu/g
Enterobacteriaceae	Absent	Petrifilm	Absent
E. Coli	Absent	Petrifilm	Absent

Storage: Store in tight, light resistant containers. Avoid exposures to direct sunlight, moisture and excessive heat.

Prepared by: Amairy Date: 3/30/2020

Quality Reviewed & Approved by: Date: 03-30-2020

Addendum B

BULK SUPPLEMENTS.com
CLEAN & PURE BULK SUPPLEMENTS

Finished Goods Specifications

Product Name	Green Tea Extract (50 % EGCG)	
Taxonomical Name	*Camellia sinensis*	
Plant part used	Leaves	
Item Code	FPGTE-02	
Item	**Specifications**	**Method**
Appearance	Brownish yellow fine powder	Organoleptic
Odor	Herbal – light scent	Organoleptic
Identification	NLT 90 %	FT-IR
Assay (as-is basis)	NLT 50 % EGCG	UV-Vis
Heavy Metals		
Arsenic	NMT 2.0 ppm	ICP-MS
Cadmium	NMT 1.0 ppm	ICP-MS
Lead	NMT 3.0 ppm	ICP-MS
Mercury	NMT 0.5 ppm	ICP-MS
Microbial Results		
Total Plate Count	NMT 10,000 cfu/g	Petrifilm
Yeast and Mold	NMT 1,000 cfu/g	Petrifilm
Total Coliform	NMT 10 cfu/g	Petrifilm
Enterobacteriaceae	ABSENT	Petrifilm
E. coli	ABSENT	Petrifilm

Prepared By: Amarilys Date: 7/16/2020

QC reviewed and approved by: Date: 07-16-2020

Hard Eight Nutrition, LLC

7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222

SAFETY DATA SHEET

Section 1: Identification

Product Name: Green Tea Extract (50% EGCG)
Chemical Name/Synonyms: N/A
Company: Hard Eight Nutrition, LLC Dba BulkSupplements.com
7511 Eastgate Road, Henderson, NV 89011 USA Telephone: 702-293-0222

In emergency call 911.
For information about this SDS, use this department contact phone#: 702-293-0222

Section 2: Hazard(s) Identification

Hazard Classification: Not a hazardous substance
Signal Word(s): N/A
Hazard Statements: N/A
Pictograms: N/A

Precautionary Statements: N/A
Description of other hazards: None

Section 3: Composition/ Information on Ingredients

Chemical Name	Chemical formula	CAS#	Conc.
Green Tea Extract (50% EGCG)	N/A	84650-60-2	N/A

Section 4: First-Aid Measures

After skin contact: Flush skin with soap and water for at least 30 minutes. Remove contaminated clothing. If symptoms develop, contact a physician.
After eye contact: Flush eyes with water for 15 minutes. Contact a physician.
After inhalation: Remove from exposure and move to fresh air immediately. Give artificial respiration if not breathing. Call a physician.
After swallowing: If conscious and alert, give 2-4 cups of water or milk. Never give anything by mouth to an unconscious person. Call a physician.

Section 5: Fire-Fighting Measures

Suitable extinguishing agents: Foam, dry powder, CO2, water spray jet.
Special Remarks on Fire Hazards: None
Special Remarks on Explosion Hazards: None

Special protective equipment for firefighters: Use personal protective equipment as required.

Section 6: Accidental Release Measures

Personal precautions: Ensure adequate ventilation, especially in confined areas. Avoid causing dust. Wear protective clothing.
Measures for environmental protection: N/A
Measures for cleaning/collecting: Take up mechanically. Rinse residues with water. Dispose of material in accordance with safety regulations.

Section 7: Handling and Storage

Handling: Wash thoroughly after handling. Minimize dust generation and accumulation.
Storage: Store under normal warehouse conditions. Store in a cool, dry place away from direct sunlight and heat.

Section 8: Exposure Controls/Personal Protection

Chemical Name	OSHA PEL	OSHA PEL (ceiling)	ACGIH OEL (TWA)	ACGIH OEL (STEL)
Green Tea Extract (50% EGCG)	None	None	None	None

General protective and hygienic measures: Minimize dust generation and accumulation. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.
Breathing equipment: Wear a respirator that meets OHOA'S 29 CFE 1910.134 and ANSI Z88.2 requirements.
Protection of hands: Wear appropriate gloves.
Eye protection: Wear appropriate eyewear.

Section 9: Physical and Chemical Properties

Form: Powder
Odor: Characteristic
Odor threshold: No data available
pH: No Data Available
Melting point/melting range: No Data Available
Boiling point/boiling range: No Data Available
Flash point: No Data Available
Evaporation rate: No Data Available
Flammability: No Data Available
Upper/lower flammability or explosive limits: No Data Available
Auto ignition temperature: No Data Available
Danger of explosion: No Data Available
Vapor pressure: No Data Available
Vapor density: No Data Available

Relative density: No Data Available
Solubility in/Miscibility with water: No Data Available

Section 10: Stability and Reactivity

Stability: Normally stable
Instability Temperature: No Data Available
Conditions of Instability: No Data Available
Incompatibility with various substances: No Data Available
Special Remarks on Reactivity: No Data Available
Special Remarks on Corrosivity: No Data Available
Polymerization: No Data Available

Section 11: Toxicological Information

Skin: No Data Available
Eyes: No Data Available
Inhalation: No Data Available
Ingestion: No Data Available
Chronic Potential Health Effects: No Data Available

Section 12: Ecological Information (non-mandatory)

Ecotoxicity: No Data Available
BOD5 and COD: No Data Available
Products of Biodegradation: No Data Available
Toxicity of the Products of Biodegradation: No Data Available
Special Remarks on the Products of Biodegradation: No Data Available

Section 13: Disposal Considerations (non-mandatory)

Chemical waste generators must determine whether a discarded chemical is classified as hazardous waste. US EPA guideline for the classification determination are listed in 40 CFR Parts 261.3. Additionally, waste generators must consult state and local hazardous waste regulations to ensure complete and accurate classification.

Section 14: Transport Information (non-mandatory)

DOT Classification: None

- **Hazard class:** No Data Available
- **Land transport ADR/RID (cross-border):** No Data Available
- **ADR/RID class:** No Data Available
- **Maritime transport IMDG:** No Data Available

Air transport ICAO-TI and IATA-DGR: No Data Available

- **ICAO/IATA Class:** No Data Available

Section 15: Regulatory Information (non-mandatory)

US Federal Regulations
SARA Section 355 (extremely hazardous substances): No Data Available
SARA Section 313 (specific toxic chemical listings): No Data Available

Clean Air Act, Section 112 Hazardous Air Pollutants (HAPs): No Data Available
TSCA (Toxic Substances Control Act): No Data Available

Section 16: Other Information

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SDS date of preparation/update: 5/3/2020

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CLEAN & PURE BULK SUPPLEMENTS

7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222 | Email: Cs@Bulksupplements.com

Certificate of Analysis

Product:	Green Tea Extract 50% EGCG		
Latin Name:	*Camellia sinensis L.*	Part Used:	Leaf
Lot Number:	1904408		
Manufacture Date:	8/22/2019	Expiration Date:	8/30/2022

Item	Specification	Results
Characteristics		
Appearance	Red brown powder	Conforms
Identity	FTIR	Conforms
Test		
Loss on drying	NMT 5.0%	4.21%
Particle size	80 mesh	Conforms
Bulk Density	Report	0.46g/ml
Heavy Metals		
Arsenic (As)	NMT 5.0 ppm	Conforms
Cadmium (Cd)	NMT 1.0 ppm	Conforms
Lead (Pb)	NMT 5.0 ppm	Conforms
Mercury (Hg)	NMT 0.2 ppm	Conforms
Microbial		
Total Plate Count	NMT 10000 cfu/g	Conforms
Yeast & Mold	NMT 1000 cfu/g	Conforms
Coliforms	Negative	Conforms
E Coli	Negative	Conforms
Salmonella	Negative	Conforms
Enterobacteriaceae	Negative	Conforms
Storage	Store in tight, light resistant containers. Avoid exposures to direct sunlight, moisture and excessive heat.	

Signature  Date 11/20/2019

Addendum C

BULK SUPPLEMENTS.com
CLEAN & PURE BULK SUPPLEMENTS

Finished Goods Specifications

Product Name	Ascorbic Acid (Vitamin C)	
Item Code	FPVTC-01	
Item	**Specifications**	**Method**
Description	White crystalline powder	Organoleptic
Odor	Slightly odorless to odorless	Organoleptic
Identification	NLT 95%	FT-IR
Assay (as-is)	NLT 98%	Titration
Heavy Metals		
Arsenic	NMT 4.0 ppm	ICP-MS
Cadmium	NMT 2.0 ppm	ICP-MS
Lead	NMT 3.0 ppm	ICP-MS
Mercury	NMT 1.0 ppm	ICP-MS
Microbiological		
Total Plate Count	NMT 1,000 cfu/g	Petrifilm
Yeast and Mold	NMT 100 cfu/g	Petrifilm
Total coliforms	NMT 10 cfu/g	Petrifilm
Enterobacteriaceae	NMT 10 cfu/g	Petrifilm
E. coli	ABSENT in 10 grams	Petrifilm

Prepared by: Amanda Ley Date: 6/18/2020

Quality Reviewed & Approved: Date: 06-18-2020

Hard Eight Nutrition, LLC

7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222

SAFETY DATA SHEET

Section 1: Identification

Product Name: L-Ascorbic acid
Chemical Name/Synonyms: Vitamin C
Company: Hard Eight Nutrition, LLC Dba BulkSupplements.com
7511 Eastgate Road, Henderson, NV 89011 USA Telephone: 702-293-0222

In emergency call 911.
For information about this SDS, use this department contact phone#: 702-293-0222

Section 2: Hazard(s) Identification

Signal Word(s): Not a hazardous substance or mixture
Hazard Statements: N/A
Pictograms: N/A
Precautionary Statements: N/A

Section 3: Composition/ Information on Ingredients

Chemical Name	Chemical formula	CAS#	Conc.
L-Ascorbic acid	$C_6H_8O_6$	50-81-7	≤ 100%

Section 4: First-Aid Measures

After skin contact: Wash off with soap and water.
After eye contact: Flush eyes with water.
After inhalation: Move to fresh air. If not breathing, give artificial respiration.
After swallowing: Never give anything by mouth to an unconscious person. Rinse mouth with water.

Section 5: Fire-Fighting Measures

Suitable extinguishing agents: Water spray, alcohol-resistant foam, dry chemical, or carbon dioxide.
Special Remarks on Fire Hazards: No data available
Special Remarks on Explosion Hazards: No data available
Special protective equipment for firefighters: Wear self-contained breathing apparatus for firefighting if necessary.

Section 6: Accidental Release Measures

Personal precautions: Avoid dust formation. Avoid breathing vapors, mist, or gas.
Measures for environmental protection: No precautions required.
Measures for cleaning/collecting: Sweep or shovel into closed containers for disposal.

Section 7: Handling and Storage

Handling: Provide appropriate exhaust ventilation at places where dust is formed.
Storage: Keep tightly closed in a dry and well-ventilated place. Light sensitive.

Section 8: Exposure Controls/Personal Protection

Engineering Controls: No data available
General protective and hygienic measures: use general industrial hygiene practice.
Breathing equipment: Wear suitable type N95 or type P1 dust masks.
Protection of hands: Use gloves prior to handling.
Eye protection: use suitable eye protection.

Section 9: Physical and Chemical Properties

Form: Solid
Color: White or clear
Odor: No data available
Odor threshold: No data available
pH: 1.0 – 2.5
Melting point/melting range: 190-194 °C (374-381 °F)
Boiling point/boiling range: No data available
Flash point: No data available
Evaporation rate: No data available
Flammability: No data available
Upper/lower flammability or explosive limits: No data available
Auto ignition temperature: No data available
Danger of explosion: No data available
Vapor pressure: No data available
Vapor density: No data available
Relative density: No data available
Solubility in/Miscibility with water: 176 g/l at 20 °C (68 °F)

Section 10: Stability and Reactivity

Stability: Stable under recommended storage conditions
Materials to avoid: Strong oxidizing agents, Extremely strong light.
Hazardous Decomposition Products: Carbon oxides
Incompatibility: Strong oxidizing agents, extremely strong light.

Section 11: Toxicological Information

Skin: No data available
Eyes: No data available
Inhalation: No data available
Ingestion: No data available

Section 12: Ecological Information (non-mandatory)

Ecotoxicity: No data available
BOD5 and COD: No data available
Products of Biodegradation: No data available
Toxicity of the Products of Biodegradation: No data available
Special Remarks on the Products of Biodegradation: No data available

Section 13: Disposal Considerations (non-mandatory)

Product

Offer surplus and non-recyclable solutions to a licensed disposal company.

Section 14: Transport Information (non-mandatory)

DOT (US)

Not dangerous goods

IMDG

Not dangerous goods

IATA

Not dangerous goods

Section 15: Regulatory Information (non-mandatory)

SARA 302 Components

No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components

This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

Section 16: Other Information

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SDS date of preparation/update: 5/3/2020

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7511 Eastgate Road, Henderson, NV 89011 USA | Telephone: 702-293-0222 | Email: Cs@Bulksupplements.com

Certificate of Analysis

Product Name	Ascorbic acid		
Bulk Supplements Lot #	2003003		
Manufacture Date	03-19-2020		
Expiration Date	03-30-2023		
Item	**Specifications**	**Method**	**Results**
Description	White crystalline powder	Organoleptic	Conforms
Identification	NLT 95 %	FT-IR	99.6 %
Assay (as-is basis)	NLT 98 %	Titration	99.2 %
Loss on drying	NMT 0.1 %	Moisture Balance	conforms
Heavy Metals			
Arsenic	NMT 1.0 ppm	ICP-MS	< 1.0 ppm
Cadmium	NMT 1.0 ppm	ICP-MS	< 0.5 ppm
Lead	NMT 0.5 ppm	ICP-MS	< 0.5 ppm
Mercury	NMT 0.1 ppm	ICP-MS	< 0.1 ppm
Microbiological			
Total Plate Count	NMT 10,000 cfu/g	Petrifilm	< 10 cfu/g
Yeast and Mold	NMT 1,000 cfu/g	Petrifilm	< 10 cfu/g
Total coliforms	NMT 10 cfu/g	Petrifilm	< 10 cfu/g
Enterobacteriaceae	Absent	Petrifilm	Absent
E. Coli	Absent	Petrifilm	Absent

Storage: Store in tight, light resistant containers. Avoid exposures to direct sunlight, moisture and excessive heat.

Prepared by: Amarilay Date: 3/31/2020

Quality Reviewed & Approved by: Date: 03-31-2020

Addendum D

Certificate of Analysis

Productname: **Cellulose Microcryst PH-102**
Inspection Report No. INS12041
Batchnumber: **20G31-U01-009671**
Quantity: 1 KG
Analyzed according to: **NF**
Expiration Date 5/15/25

Tests	Requirement	Result	Unit	Standard remark
Description	Fine, white or almost white powder	Conforms		Fagron US
Solubility	Insoluble in water	Conforms		Fagron US
Identification A	Conforms	Conforms		USP, Iodinated zinc chloride solution
Identification B	Conforms	Conforms		Degree of polymerization
Degree of polymerization	<= 350	237	units	Viscosity - Capillary Methods <911>
Residue on ignition	<= 0.1	0.1	%	Residue on Ignition <281>
Conductivity	<= 75	56	µS/cm	USP Monograph
pH	5.0 - 7.5	6.5		<791>
Loss on drying	<= 7.0	4.3	%	Loss on Drying <731>
Bulk density	0.27 - 0.34	0.31	g/mL	USP Monograph
Water-soluble substances	<= 0.25	0.16	%	USP Monograph
Ether-soluble substances	<= 0.05	0.02	%	USP Monograph
Total aerobic microbial count	<= 1000	Conforms	cfu/g	Microbial Enumeration Tests <61>
Total yeasts and molds count	<= 100	Conforms	cfu/g	Microbial Enumeration Tests <61>
Tests for specified organisms	Staphylococcus aureus	Conforms		Tests for Specified Microorganisms <62>
Tests for specified organisms	Pseudomonas aeruginosa	Conforms		Tests for Specified Microorganisms <62>
Test for specific organisms	E.Coli	Conforms		Tests for Specified Microorganisms <62>
Tests for specified organisms	Salmonella	Conforms		Tests for Specified Microorganisms <62>
Elemental Impurities	Conforms	Conforms		<232>, <233>
Residual solvents	Conforms	Conforms		Residual Solvents <467>

Fagron, Inc. - 2400 Pilot Knob Road - St. Paul, MN 55120 - USA
Tel. (800) 423 6967 - Fax (800) 339 1596 - info@fagron.us

Certificate of Analysis

Productname:	**Cellulose Microcryst PH-102**
Inspection Report No.	INS12041
Batchnumber:	**20G31-U01-009671**
Quantity:	1 KG
Analyzed according to:	**NF**
Expiration Date	5/15/25

Tests	Requirement	Result	Unit	Standard remark

Release:
Julie Lentz
Quality Assurance
Technician

Conclusion Date: 3/17/21

Conclusion: APPROVED

This document has been produced electronically from our quality system and is valid without signature.