Feasibility Pilot Clinical Trial of Omega-3 (EPA+DHA) Supplement vs. Placebo for Post-Acute Sequelae of COVID-19 Recovery among Health Care Workers

Short Title: Covid Recovery Study
Investigational Product: OceanBlue Omega-3 EPA+DHA Supplement (KD Pharma)
Principal Investigator: Arunima Sarkar, MD, FACP, CMD - HMH Center for Healthy Senior Living

Sub-Investigators:

- Manisha Parulekar, MD – HMH Center for Healthy Senior Living, Dept. of Geriatrics
- Chinwe Ogedegbe, MD, MPH, FACEP
- Portia Chinnery, BSN, RN, CEN, CPPS
- Erin Speiser, PhD, MA, CCRP

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1.0 Study Summary

Study Title	HMH Omega-3 Covid Recovery Study
Study Design	We will conduct a two-arm, double blind randomized 12-week study to supplement omega-3 (EPA + DHA) among 100 adults (age 18+) who had covid-19 and are experiencing possible after-effects from the illness (post-acute sequelae of covid-19, also called post-covid syndrome or long covid syndrome).
Primary Objective	The primary objective is to serve as a feasibility study for omega-3 fatty acid supplementation v. placebo in adult patients to limit long covid syndrome. This will serve as a proof-of-concept for a larger follow-up study to subsequently be conducted.
Secondary Objective(s)	Determine which of the post-covid symptom(s) are most impacted by omega-3 supplement.
Research Intervention(s)/ Investigational Agent(s)	Participants will be assigned to one of two study arms and asked to take an Omega-3 supplement or placebo for 12 weeks. Participants will report symptoms bi-weekly throughout the study period. A spot blood sample to assess omega-3 levels will be done at baseline and at the end of the 12-week study period. A survey will be used bi-weekly to assess health status and outcomes via patient self-report. Data on demographics and comorbidities such as obesity and diabetes will be collected at baseline. At the end of study participation, subjects will take a follow-up survey assessing feasibility.
IND/IDE #	IND # 157250
Study Population	Hackensack Meridian Health team members age 18+ who tested positive for COVID-19 28+ days prior and who are not already taking an Omega-3 supplement.
Sample Size	50 participants in each arm = 100 total for final analysis (up to 60 participants in each arm will be recruited if needed, dependent on attrition for a total of up to 120)
Study Duration for individual participants	Individual participants will be in the study for 12 weeks. During the 12 week study period, subjects will be sent a survey every two weeks. At the end of the 12 weeks, subjects will complete a short survey collecting feasibility and acceptability data.
Study Specific Abbreviations/ Definitions	● Hackensack Meridian Health (HMH) ● Center for Healthy Senior Living (CHSL)

2.0 Objectives

Primary Objective

To determine the feasibility of a clinical trial for omega-3 supplementation v. placebo in medical center team members for post-covid recovery.

This will serve as a proof-of-concept for a future, grant-funded study to evaluate the efficacy of omega-3 supplementation among a larger population recovering from covid-19.

Secondary Objective

To determine which symptoms of long covid syndrome (if any) are most affected by taking an omega-3 supplement.

3.0 Background

Supplement Interventions for Recovery of Post-Acute Sequelae of Covid-19 (Long Covid Syndrome)

Since COVID-19 launched a worldwide pandemic in December 2019, non-prescription interventions have been and continue to be explored to limit the effects of the virus. As COVID-19 is novel, few studies on nutritional interventions have been completed. Much of the literature focuses on the breadth of possible or potential nutrition-based measures, including dietary protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, iron, zinc, and selenium [1]. Numerous analyses focus on Vitamin D, Vitamin C, and zinc [2,3,4]. Vit. D has been found to inhibit viral replication and have anti-inflammatory and immune-modulating effects, but as with other supplements used for prophylaxis, controlled trials specific to COVID-19 are needed [2, 4]. One longitudinal study in the UK, announced in June 2020, is examining Vit D status of 12,000 adults over the 2020-21 winter and will include a sub-analysis to determine if minority ethnic groups are more adversely affected [4]. Another study suggests that 2,000-5,000 IU of Vitamin D daily for older adults with Parkinson's disease (PD) may slow PD progression and have a protective effect against COVID-19 [5]. All of these studies, however, address active covid-19 infection, not the potentially long recovery period afterwards that is gaining worldwide attention.

The NIH has termed this symptomatic recovery period "Post-acute Sequelae of Covid-19" or "Long Covid Syndrome." To address this, NIH held its first workshop dedicated to the topic in December 2020 [6]. From severe hospitalized cases to mild outpatient cases, the road to recovery is complex and not yet well understood, though a few studies published thus far provide insights and researchers are beginning to study what interventions may be beneficial.

These patients, also known as long-haulers or those with post covid syndrome, have been shown to suffer from after-effects for 12+ weeks after contracting the virus. Effects may be most severe in patients with underlying lung disease such as asthma and/or who had a more severe form of covid-19, including those hospitalized. However, even

those having initially recovered from a mild case of the virus report long-term effects [7].

Long-term effects of covid-19 include loss of taste, loss of smell, continued need for oxygen therapy, and more. One New Jersey-based study on 183 patients from Hackensack University Medical Center found that at 35 days after discharge from the hospital following treatment for covid-19, 55% reported fatigue, 45.3% dyspnea, and 51% muscular pain, among other symptoms [8]. For some, post-covid syndrome lasts several weeks, while for others it may last several months. A small number of patients are thought to perhaps never return back to their pre-covid baseline.

According to the Mayo Clinic [7], the most common signs and symptoms of long covid syndrome are:

- Fatigue
- Shortness of breath
- Cough
- Joint pain
- Chest pain

Mayo Clinic states other long-term signs and symptoms may include: [7]

- Muscle pain or headache
- Fast or pounding heartbeat
- Loss of smell or taste
- Memory, concentration or sleep problems
- Rash or hair loss
- Organ damage, in particular:
    - “Heart. Imaging tests taken months after recovery from COVID-19 have shown lasting damage to the heart muscle, even in people who experienced only mild COVID-19 symptoms. This may increase the risk of heart failure or other heart complications in the future.
    - Lungs. The type of pneumonia often associated with COVID-19 can cause long-standing damage to the tiny air sacs (alveoli) in the lungs. The resulting scar tissue can lead to long-term breathing problems.
    - Brain. Even in young people, COVID-19 can cause strokes, seizures and Guillain-Barre syndrome — a condition that causes temporary paralysis. COVID-19 may also increase the risk of developing Parkinson's disease and Alzheimer's disease.” [7]

- Blood clots and blood vessel issues
    - “COVID-19 can make blood cells more likely to clump up and form clots. While large clots can cause heart attacks and strokes, much of the heart damage caused by COVID-19 is believed to stem from very small clots that block tiny blood vessels (capillaries) in the heart muscle.
    - Other parts of the body affected by blood clots include the lungs, legs, liver and kidneys. COVID-19 can also weaken blood vessels and cause

them to leak, which contributes to potentially long-lasting problems with the liver and kidneys." [7]

- Mood and fatigue issues
    - "People who have severe symptoms of COVID-19 often have to be treated in a hospital's intensive care unit, with mechanical assistance such as ventilators to breathe. Simply surviving this experience can make a person more likely to later develop post-traumatic stress syndrome, depression and anxiety.
    - Because it's difficult to predict long-term outcomes from the new COVID-19 virus, scientists are looking at the long-term effects seen in related viruses, such as the virus that causes severe acute respiratory syndrome (SARS).
    - Many people who have recovered from SARS have gone on to develop chronic fatigue syndrome, a complex disorder characterized by extreme fatigue that worsens with physical or mental activity, but doesn't improve with rest. The same may be true for people who have had COVID-19." [7]

It must be noted that other long-term health effects of covid-19 are continually being discovered, so the list of symptoms may change over time. A UK study of 100 patients who recovered from covid-19 found that 4-8 weeks after hospital discharge, 72% of those who had been in the ICU reported ongoing fatigue, breathlessness (65.6%), psychological distress (46.9%) and a 68.8% drop in EQ5D (quality of life). For those not in the ICU, 60.3% reported continued fatigue, breathlessness (42.6%), psychological distress (23.5%) and a 45.6% reduction in EQ5D [9]. A study in France of 120 patients hospitalized for covid and studied approximately 110 days after admission, found that the "most frequently reported persistent symptoms were fatigue (55%), dyspnoea (42%), loss of memory (34%), concentration and sleep disorders (28% and 30.8%, respectively)" [10]. There were no statistically significant differences between ICU and non-ICU patients. Measures of mobility, self-care, pain, anxiety or depression and usual activity were also similar, except for a "slight difference in pain in the ICU group" [10].

Even in younger (age 18-34) patients who were never hospitalized, a CDC phone survey found 1 in 5 were not back to their previous healthy state 14-21 days after testing positive [11].

Inflammation may be a common thread with multiple effects from long covid syndrome. A common complaint is "brain fog" or challenges with thinking clearly, which may be related to post-covid fatigue linked to ongoing inflammation [12]. Physicians report ongoing inflammation of the brain and nervous system, resulting in a cascade of effects including toxicity and dysregulation [13]. One of the more prevalent effects is seen in a study reported in JAMA Cardiology. It found 78 of 100 recently recovered covid patients in Germany had cardiac issues as seen on cardiovascular magnetic resonance (CMR) imaging, while 60 had ongoing myocardial inflammation [14].

One of the challenges with long covid syndrome is that the length of time it lasts is not

yet known, and could span from weeks to years [12]. A study of 143 patients in Rome, Italy who had been hospitalized with covid and recovered, found that 87.4% had at least one persistent symptom [15]. In particular, 53.1% still reported fatigue, 43.4% had dyspnea (breathing difficulties), 27.3% reported joint pain, and 21.7% had chest pain [15].

The Rome-based study team, located at the Fondazione Policlinico Universitario A. Gemelli IRCSS, asserts that geriatricians are best able to manage the multidisciplinary needs of post-covid patients: “In fact, the geriatrician is the specialist who best can manage the multidimensional health problems, with a great aptitude and skill to cope multimorbid and complex patients. Second, geriatricians are the doctors who best know the principles of teamwork in close collaboration with the other health care professionals and family. In particular, the geriatrician is able to manage the onset of the most important syndromes, such as sarcopenia, malnutrition, depression, and delirium.” [16]

The study outlined in this protocol is managed by a geriatric team from the Center for Healthy Senior Living (CHSL) at Hackensack University Medical Center in Hackensack, New Jersey.

Omega-3 Supplementation

The Covid-19 infection is characterized by a very strong inflammatory response of the body and often results in a “Covid-19 pneumonia”, similar to what is known as Acute Respiratory Distress Syndrome (ARDS). Pharmacotherapies that moderate inflammation in ARDS/Covid-19 pneumonia are lacking.

It is known that Covid-19 infection can cause severe pneumonia inflammation, triggering a pro-inflammatory “cytokine storm” expressed through a high expression of IL-6 and tumor necrosis factor (TNF), subsequent release of pro-inflammatory prostaglandin E2 (PG), 5-lipoxygenase (LOX) and leukotrienes. High levels of free nitric oxide (NO)-radicals causing oxidative stress and damage to the cell tissue. Additionally, at the late stage of the disease, neo angiogenesis has been seen to be a crucial step of lung fibrosis, leading finally to a fatal ARDS condition.

The effects of omega-3 fatty acids, in particular EPA, on the many different inflammatory pathways have been well studied and described in the literature [17]. Many of these papers discuss the anti-inflammatory effects of the omega-3 fatty acids in relation to cancer development and treatment [17] and inflammatory bowel disease such as ulcerative colitis. Although these inflammatory disorders have nothing to do with Covid-19, the basic principle of inflammatory response and anti-inflammatory pathways within our body cells is highly likely to be the same, whether we focus on ulcerative colitis, colon cancer, rheumatoid arthritis or “Covid-19 pneumonia”.

It is well known that the pro-inflammatory eicosanoids are derived from a polyunsaturated omega-6 fatty acid called Arachidonic Acid (AA) through the

cyclooxygenase (COX-), LOX- and p450 epoxygenase pathway. These pro-inflammatory eicosanoids:

- increase the vascular permeability
- promote platelet aggregation
- recruit neutrophils
- cause edema
- release pro-inflammatory substrates such as cytokines which in turn lead to the production of chronic inflammatory mediators like IL-1ß, IL-6, IL-8 and TNFα

The same COX and LOX enzyme-systems are responsible for converting the omega-6 arachidonic acid into pro-inflammatory eicosanoids or alternatively the omega-3 EPA into anti-inflammatory eicosanoids. Thus, there is a strong competitive interaction between the AA and EPA with COX- or LOX enzyme systems in the body cells. If the concentration of AA is dominant, then more pro-inflammatory eicosanoids are generated. However, if there is more EPA present, then more anti-inflammatory eicosanoids are produced and the intensity of an inflammatory attack is reduced.
Both AA and EPA originate from our diet. A diet rich in red meat, milk, milk products, cheese and eggs combined with the use of omega-6 rich vegetable oils like sunflower or corn oil will result in a high concentration of pro-inflammatory arachidonic acid in the cell membranes. A diet rich in fatty fish (sardines, anchovy, salmon, mackerel, tuna) in combination with neutral vegetable oils like olive oil will result in a more equilibrated ratio of omega-6 to omega-3 in the cell membranes. EPA partly displaces AA in our cell membranes [18,19] and reduces the formation of pro-inflammatory cytokines [20].

Rationale

Marine derived omega-3 polyunsaturated fatty acids (PUFA) supplementation have been shown to have a significant lowering effect on C-reactive protein, IL-6 and TNF which slows down the AA cleavage from the cell membrane and subsequent synthesis of COX/LOX generated pro-inflammatory eicosanoids [21]. Furthermore, by downregulating the NFkß with help of the EPA dependent IKKß-complex not only less IL-6 is expressed but also less vascular endothelial growth factor (VGEF), which in turns reduces the neo angiogenesis activity, a suppression highly desired during the Covid-19 pneumonia infection, and which may be beneficial in reducing ongoing symptoms of post-covid syndrome**.**

Nitric oxide (NO), a free radical derived from L-arginine by nitric-oxide-synthase (NOS) is proposed to play an important role in many inflammation processes and leads to severe inflammation related tissue damage. The oxidative stress triggered by NO may also additionally activate NFkß [22] and in turn increase further the “inflammatory storm”. Omega-3 fatty acids, in particular EPA, is involved in several different metabolic pathways which down-regulate the NOS gene expression, resulting in a decreased NO production thus tissue damage [23]. Another important point of inflammatory down-regulation by EPA is competitive regulation of the COX-2 system. If the cell membrane contains a high content of EPA, then the probability that an EPA molecule connects with

the COX-2 system and generates anti-inflammatory eicosanoids is much higher than in the case that the pro-inflammatory AA dominates in the cell membrane [24].

Additionally, EPA is converted in the body to very potent pro-resolving mediators (PRMs) known as resolvins, protectins and maresins. These very active compounds reduce the magnitude and duration of inflammation, stimulate wound healing and regenerate damaged tissue.

ARDS and ICU studies [25, 26, 27] of immunonutrition with omega-3 (enteral supplementation) after the start of hospitalization showed positive results within two weeks. A significant reduction in pro-inflammatory eicosanoids was evident after 24 hours [25]. In this study, the patients received during a period of 12 hours an enteral nutritional supplement containing 10% fish oil. The administered dose was 0.12g/kg/h. Taking into consideration an average body weight of 75kg, the patients would have received, within the 12-hour supplementation period, a total of approximately 3 g Omega-3 of which roughly 2 g would have been EPA in the natural triglyceride form. Numerous other studies discussed in [26, 27, 28] also indicated clear benefits of an Omega-3/fish oil treatment for hospitalized ARDS patients, including a reduced mortality. The effects on long-term symptoms from covid-19 are just beginning to be explored among researchers, making this study among the first.

Considerations for COVID-19 among Healthcare Workers in New Jersey

As the densest state in America, New Jersey has been particularly hard-hit by coronavirus cases [29]. With 516,608 confirmed cases statewide as of January 8, 2021, those over age 65 have been greatly affected, comprising 16.8% of cases [30] and 79.8% of the state's 17,587 lab-confirmed deaths as of January 7, 2021 [30].

Healthcare workers – the subject of this study – have also been devastated by the virus. A study of NJ healthcare workers (HCW) early in the pandemic found that these employees were at greater risk for becoming infected than non-healthcare workers [31]. A 7.3% prevalence of infection was found among NJ healthcare workers versus 0.4% among non-healthcare workers [31]. Infections were particularly high among Black, Latino and "other" races [31]. The study acknowledged that further research is needed "to examine whether racial differences in COVID-19 among HCW may be related to their particular roles in the health care setting or are reflective of residence in communities that are more vulnerable to infection."[31] More recent news attests to NJ team members continuing to fall ill, including over 100 at Hackensack Meridian Ocean Medical Center in December 2020 [32]. Statistical analysis in our study will examine demographic information such as race and occupational role.

4.0 Study Endpoints

4.1 Primary Outcome Variables

The primary endpoint is evaluation of feasibility and acceptability of omega-3

supplementation v. placebo to limit post-covid syndrome among adult patients. The Follow-up Feasibility Survey (Appendix D) will be used for this analysis.

4.2 Secondary and Exploratory Outcome Variables
A separate analysis will be conducted to determine which post-covid symptom(s) are more impacted by omega-3 supplement. The Bi-weekly Symptoms and Quality of Life Post Covid-19 Survey (Appendix C) includes the four symptoms being measured (respiratory, fatigue, lack of taste, lack of smell). Therefore, this bi-weekly survey will be used for this efficacy analysis.

5.0 Study Intervention / Investigational Agent
The investigational product is EPA+DHA, an omega-3 supplement manufactured by KD Pharma.

6.0 Procedures Involved

6.1 Study Design
This is a double-blind, randomized controlled trial (RCT) with two treatment arms:
Arm 1 - Omega-3 (EPA+DHA) – Dose is 2,100mg per day via 3 mini-capsules, 2x/day (a total of 6 mini-capsules per day). Each capsule has 252mg of EPA and 102mg of DHA.

Support for dosing:
- The American Heart Association (AHA) says taking up to 3 grams of fish oil daily in supplement form is considered safe [33]
- Up to 5,000mg of omega-3 fatty acids per day is considered safe [34].
- The U.S. Food and Drug Administration recommends consuming no more than 3 g/day of EPA and DHA combined, including up to 2 g/day from dietary supplements.[35]

Arm 2 - Placebo – made from soybean oil (same dosing schedule as intervention arm)

Supplement and placebo will be supplied by KD Pharma.

6.2 Research Procedures

For an overview of the study, please see figure 1 below.

1. Team members who email the study team at the address on the flyer will be sent an eligibility survey in REDCap to determine if study inclusion criteria are met.

2. Those who meet study inclusion criteria will then be sent the study consent form in REDCap, and encouraged to call or email the study team with questions.

3. If the patient expresses further interest in study participation, s/he will be consented via REDCap and then will be sent a link to the baseline survey in REDCap.

4. Upon consent, RC will assign ID# and enter the subject into REDCap (study data management system).

5. Subjects will be randomly assigned to receive 3 Omega-3 (EPA+DHA) mini-capsules twice daily (total of 2,100mg per day) for 12 weeks in the experimental intervention arm or three placebo mini-capsules twice daily for 12 weeks.

- Study supplement or placebo are supplied at no cost to the subject and will be mailed to the subject's home.
- Study subjects will receive two shipments over the course of study participation.
    - Package 1 upon enrollment
    - Package 2 at the end of week 4
- Subjects will also receive, in these shipments, two spot blood sample tests for omega-3 levels, and directions indicating when to use the test kits.

6. All study subjects in each arm will be asked to give a spot sample (2 drops) of blood at baseline and again after 12 weeks (end of study participation). This will be done using OmegaQuant test kits that are mailed to the subject's home. The de-identified samples will be mailed by the subject in the provided envelope to OmegaQuant Lab, associated with University of South Dakota Medical Center, for analysis of omega-3 levels. These tests involve no cost to the subject. Subjects will be informed of their omega-3 level after results are returned from the lab and the subject's participation in the study is complete.

7. Monitoring of Subjects:

- Subjects will be encouraged to call RC at any time with study questions. RC will also call each subject weekly to ensure procedures are being followed and answer any questions. The weekly "check-in call" will occur for 12 weeks.

- Each subject will be checking their blood pressure. Subjects will report their blood pressure via REDCap in their bi-weekly survey. Reported adverse events will be documented.

- Subjects in both arms will be tracked for 3 months (12 weeks). An interim analysis will be done for a sub-sample (the first 20 subjects) after three weeks of participation to determine if any arm should be adjusted or terminated.

- Participants will continue to receive standard of care and follow up for any routine conditions being managed at HackensackUMC.

8. The final study activity will include the 2nd spot blood sample and a short survey (survey link emailed to subject via REDCap) to collect feasibility and acceptability data. The survey will take about 10 minutes to complete.

9. Subjects will then be mailed a $40 gift card for completing the study.

10. Subjects will be informed of their omega-3 level after results are returned from the lab and the subject's participation in the study is complete

Any subject missing both daily doses 3 times a week for 3 weeks in a row will be removed from the study for non-compliance, and asked to dispose of any unused study supplement/placebo. This will be documented in a dedicated RedCap survey for anyone who discontinues study participation, either for non-compliance or of their own will.

Any subject who has another covid-19 infection during study participation may continue on the study. The RC will inform the subject of this if/when any subject reports a new covid infection.

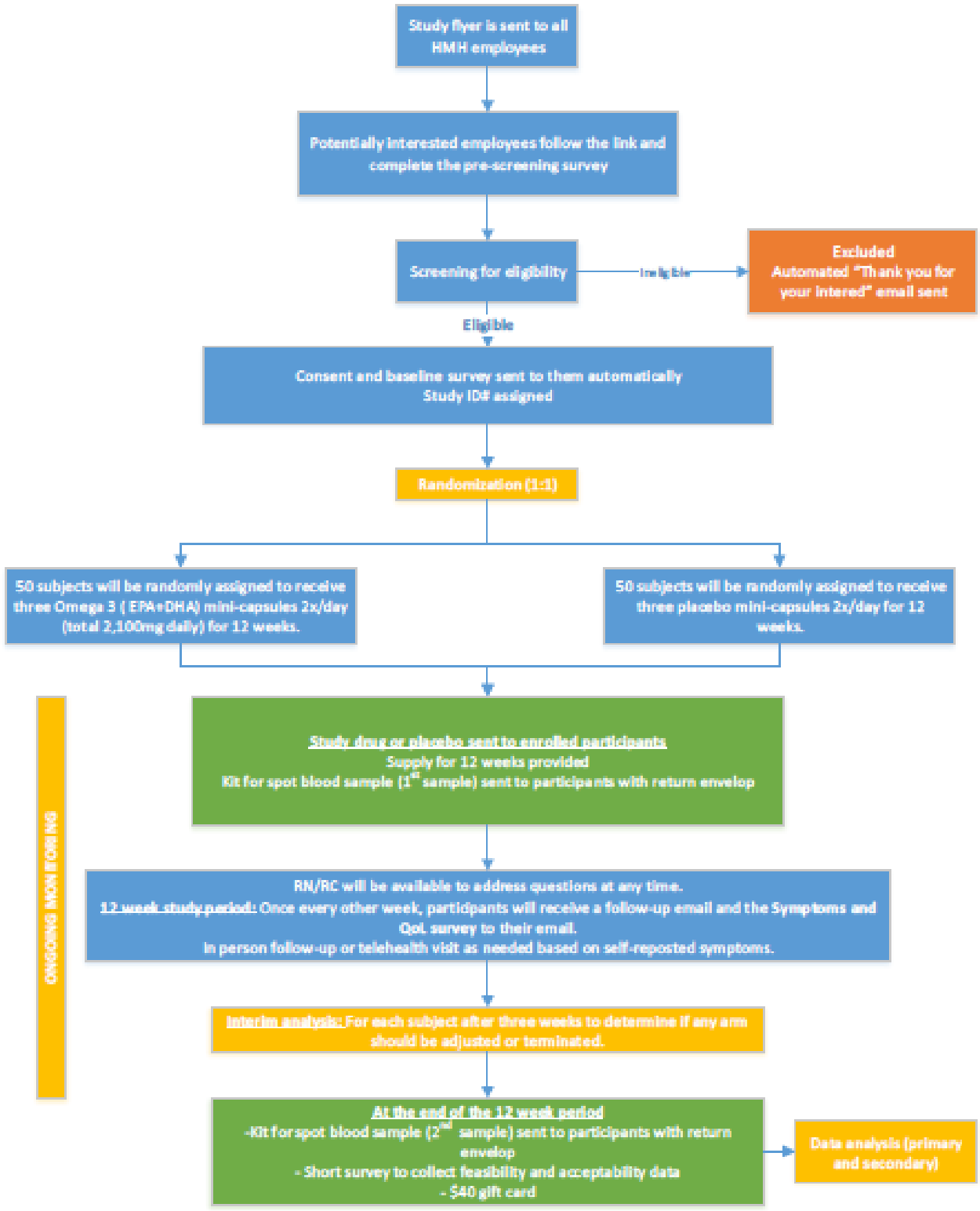

Figure 1: Study Schema

7.0 Data and Specimen Banking

7.1 Data or specimens for future use

Each subject will have two blood specimens collected for analysis of omega-3 levels. Those specimens will not be banked for future use after this study.

Data collected from questionnaires will be stored on the HMH REDCap database on the HMH server. Data will be stored for six years after the end of the study. Access to the data will be restricted to the study staff.

7.2 Data to be stored or associated with each specimen

For each subject who has the 2 blood specimens taken, only the test result will be stored – together with the other study data - for six years per HMH policy. As the consent form indicates, “Spot blood samples will not be used for future research. The samples will be destroyed by Omega Quant Labs approximately two weeks after analysis.”

7.3 Procedures to release data or specimens

In order to access data, a research proposal that describes the intended use of the data must be submitted and approved by the PI. Anyone requesting access to data must obtain IRB approval and demonstrate secure data storage prior to receiving a de-identified data set. Access to the data is limited to non-commercial use.

8.0 Sharing of Results with Subjects

Individual-level data (the results of both COVID-19 tests and the omega-3 levels from the blood draw if applicable) will be shared with participants. The major findings of the study and aggregate data, will be shared with participants after the study has concluded.

1) Unblinding will occur when a subject drops out of the study due to an adverse event. The subject will be informed of their study arm assignment via email so that they can better understand any possible adverse reaction to the study medication.

2) Subjects who complete the study will be unblinded and informed of their study arm assignment via email after the study team has seen their data (descriptive statistics generated by RedCap). This will be done within 4 weeks of each subject finishing the study.

The study coordinator will inform each subject when they finish study participation, to expect an email advising which study arm they were in.

9.0 Study Timelines

Each subject will spend 12 weeks in the study.
It is anticipated that all subjects will be enrolled within a 6-month timeframe.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
IRB approvals & startup	X	X	X									
Enroll-ment				X	X	X	X	X	X			
Subjects on study (12 weeks)				X	X	X	X	X	X	X	X	X
Interim analysis at 3 weeks					X							
Final data analysis										X	X	X

10.0 Inclusion and Exclusion Criteria

Inclusion Criteria

- Team member at Hackensack Meridian Health
- Age: 18+
- Willing to provide informed consent
- Formal diagnosis of COVID-19 via PCR test (if home test was done, team member must confirm via PCR test)
-Outpatient treatment only for covid-19; no hospitalization (most team members will be vaccinated and may likely have milder case)
- Must be experiencing 1+ ongoing covid-19 symptom being measured in this study (respiratory symptoms (shortness of breath, cough), fatigue, loss of taste, loss of smell)
-Symptom(s) have persisted for more than 12 weeks after initial infection

-Symptom(s) coincided with covid-19 infection and were not present prior to covid-19 infection
- Does not have soy allergy
- Does not have allergy to fish
- Able to participate in bi-weekly surveys in REDCap
- Able to take own blood pressure and record it in bi-weekly REDCap survey
- Willing to participate in 12-week study and be assigned to either intervention or placebo arm
- Not currently taking an omega-3 supplement or other high-dose supplement (over 2,000 IU) with potential for aiding recovery of long covid syndrome (e.g. zinc, Vit C, Elderberry).
-Able to take/swallow six mini-pills daily
-Able and willing to give a spot blood sample (2 drops) at baseline and end of study.

Exclusion Criteria
- Not a Team Member at Hackensack Meridian Health
- Not age 18+
- Unwilling to provide informed consent/ declined to take part
- No formal diagnosis of COVID-19 via PCR test (if home test was done, team member must confirm via PCR test)
-Were hospitalized for treatment of covid-19
- Not experiencing 1+ ongoing covid-19 symptom being measured in this study (respiratory symptoms (shortness of breath, cough), fatigue, loss of taste, loss of smell)
-Symptom(s) have persisted for more than 12 weeks after initial infection
-Symptom(s) did not coincide with covid-19 infection and were present prior to covid-19 infection
- Does have soy allergy
- Does have allergy to fish
- Not able to participate in bi-weekly surveys in REDCap
- Not able to take own blood pressure and record it in bi-weekly REDCap survey
- Not willing to participate in 12-week study and be assigned to either intervention or placebo arm
- Currently taking an omega-3 supplement or other high-dose supplement (over 2,000 IU) with potential for aiding recovery of long covid syndrome (e.g. zinc, Vit C, Elderberry).
-Unable to take/swallow six mini-pills daily
-Not able and not willing to give a spot blood sample (2 drops) at baseline and end of study.

11.0 Vulnerable Populations
Subjects will be age 18+ and must be actively employed by HMH in order to participate in the study.

Hackensack Meridian *Health* is dedicated to creating an inclusive environment that delivers culturally competent, patient-centered care. We value and celebrate the contribution of our team members and acknowledge that everyone deserves to be treated with dignity and respect.Through the Diversity & Inclusion program, we strive to:

- Foster an inclusive environment that embraces different perspectives and that values the contributions of each individual
- Promote diversity at every level throughout our network
- Employ and develop the finest talent from all groups within our vibrant communities
- Provide outstanding and award-winning health care services

Through the Team Member Resource Group (TMRG) strategic initiative of Diversity & Inclusion, team members can link up with coworkers from similar backgrounds and identities to make a difference in the workplace and help achieve their goals. Current TMRGs include the Multiracial Resource Group, Aspiring Women Leaders, Women in Leadership, Pride & Allies, Veterans, and Young Professionals.

To foster diversity in study enrollment, the recruitment flyer will be sent specifically to these TMRGs for targeted distribution.

12.0 Local Number of Subjects
The number of subjects will be 50 in each of two arms, for a total of 100 subjects for analysis. Up to 60 participants in each arm will be recruited if needed, dependent on attrition, for a total of up to 120 subjects.

Study Site(s)
Research activities will take place remotely as indicated. Specifically, subjects will:
-have study meds delivered to them
-will complete eConsent in REDCap
-will have the omega-3 level test kits mailed to their home, will complete the spot blood sample at home and mail directly back to OmegaQuant Lab in the mailing envelope provided.

13.0 Recruitment Methods
Eligible participants will be identified among adult (age 18+) team members working for Hackensack Meridian Health. A recruitment flyer will be sent to all team members via HMH employee newsletters including "The Pulse" and "One." Additionally, to foster diversity in study enrollment, the recruitment flyer will be sent to the Team Member Resource Groups (TMRGs) at HMH for targeted distribution to help ensure diversity in enrollment, as noted in Section 11.0.

The flyer will also be placed in physician lounges across the HMH network.

To further expand recruitment, the study flyer will be given to the HMH Covid Call Center so team members who are experiencing long covid symptoms can be provided with the study email address. Those who receive the email address may contact the study team or not per their preference, and will not be followed up on by the Covid Call Center.

Each potential subject will access a link to an eligibility survey to determine if they meet inclusion criteria.

They will be given the opportunity to ask any questions by contacting a member of the study team. If the team member is interested, they will access the informed consent form in REDCap and be asked to either sign it and participate or download a copy to review on their own time. If they later choose to participate, they can continue with informed consent in REDCap.

Alternatives to participation include that subjects may choose to consult their healthcare provider for help addressing their symptoms. Subjects may also take a supplement(s) on their own at any time.

14.0 Withdrawal of Subjects

If a subject needs to be withdrawn from the study without their consent for medical reasons or non-compliance, she or he will be notified by Dr. Sarkar or Dr. Parulekar by phone, with a follow-up letter mailed to the subject's home.
If a subject chooses to withdraw from the study, she or he must notify the PI by calling the phone number on the consent form. All data collected up to the point of termination will be kept in the study.

Any subject missing both daily doses 3 times a week for 3 weeks in a row will be removed from the study for non-compliance, and asked to dispose of any unused study supplement/placebo.

15.0 Risks to Subjects and Monitoring Plan

<u>8 Possible Risks from Omega-3 Supplement:</u>
<u>Risk #1</u>: Taking large amounts of fish oil can inhibit blood clot formation, which may increase the risk of bleeding and cause symptoms such as nosebleeds or bleeding gums

<u>Outcome</u> - Fish oil supplementation did not increase perioperative bleeding [36]

<u>Outcome</u> - The present overview found no support for discontinuing the use of n-3 fatty acid treatment before invasive procedures or when given in combination with other agents that affect bleeding [37].

<u>Monitoring Plan for bleeding risk</u>: *Plan: As bleeding risk is low, we do not need to adjust any medications. We will add a follow up question for each subject, asking: "any bleeding?"*

Risk #2: One small study, for example, found that taking 8 grams of omega-3 fatty acids per day led to a 22% increase in blood sugar levels in people with type 2 diabetes over an eight-week period [38].

Taking high doses of omega-3 fatty acids can stimulate glucose production, which may lead to increased blood sugar — though the scientific evidence is not conclusive.

Monitoring Plan for Hyperglycemia risk: *Chance is low so no need of adjustment of medication required, so we can skip extra monitoring*

Outcome - Findings from RCT trials suggest that omega-3 supplementation was unable to affect either plasma glucose levels or HbA1c except increased fasting glucose levels in Asians [39]

Risk #3: Omega-3 fatty acids have been shown to lower blood pressure, which may interfere with certain medications and cause problems for those with low blood pressure

An analysis of 31 studies concluded that taking fish oil can effectively lower blood pressure, especially for those with high blood pressure or high cholesterol levels [40].

Monitoring Plan for Hypotension risk: *No significant drop to adjust medication. Subject will be asked to self-monitor blood pressure and report it in the bi-weekly survey in REDCap. This RedCap survey also includes a question asking team members to indicate the method used to take their blood pressure: "BP was taken by machine at home" or "BP was taken by machine at a pharmacy" or "BP was taken manually in medical office."*

Outcome: The meta-analysis also found that among all participants who received omega-3s, through supplements such as fish oil, the average decrease in systolic pressure was 1.75 mm Hg and diastolic pressure dropped by 1.1 mm Hg, regardless of the person's blood pressure status [41].

Risk #4: Diarrhea is a side effect of omega-3 fatty acid supplements such as fish oil and flaxseed oil [42].

Monitoring Plan for Diarrhea risk: there is risk of diarrhea with omega-3, taking supplements with meals and consider decreasing dosage to see if symptoms persist. *Will recommend that supplement/placebo be taken with food.* [43]

Risk #5: Fish oil is high in fat and may cause acid reflux symptoms such as belching, nausea, indigestion and heartburn in some people [44].

Monitoring Plan for GERD risk: *Plan: splitting dose into a few smaller portions throughout the day may help eliminate indigestion*

Risk #6: Some animal studies have found that a high intake of omega-3 fatty acids could increase the risk of hemorrhagic stroke while other human studies have found no association [43]

Monitoring Plan for Hemorrhagic stroke: not proved in humans, so will not use this for our study

Risk #7: Caution---Certain types of omega-3 fatty acid supplements like cod liver oil are high in vitamin A, which can be toxic if consumed in large amounts

Monitoring Plan for Vitamin A hypervitaminosis: based on composition, we can also remove this based on our Omega 3 supplement

Risk #8: Although moderate doses of fish oil have been shown to improve sleep quality, one case study suggests that taking large amounts caused insomnia [43].

Monitoring Plan for Insomnia: not including, as there is not enough evidence

Summary of monitoring plan for side effects:

1. Self-reported BP check, submitted via bi-weekly survey, using a BP machine at home, BP machine at a pharmacy, or manually in medical office (will indicate method on bi-weekly survey)
2. Take omega 3 with meals to reduce diarrhea
3. Ask question “any increased bleeding?” during weekly check-in call

Note: Consent form will include that some interactions may occur with anticoagulants, and antihypertensive medications, though minimal. The consent form will also include that the finger prick spot blood test for omega-3 levels may cause minor soreness on the subject's finger.

Additionally:
EPA+ DHA is an omega-3 supplement, which are generally regarded as safe when given orally. Omega-3 products are approved for use in the treatment of post myocardial infarction, hypertriglyceridemia and as a dietary supplement in numerous territories worldwide, including Europe and the US.

Experience with the approved preparations and clinical studies is that adverse events are relatively minor in nature and severity, and are primarily related to gastro-intestinal effects.

During the study the subject will take a health survey bi-weekly and will be asked to report any health concerns to the PI. Reported adverse events will be documented. Additionally, the Research Coordinator (RC) will also call each subject weekly for the

duration of the study (total of 12 weeks) to ensure procedures are being followed, answer any questions, and refer any health issues to the PI.

- If any individual subject experiences an adverse event (AE), the PI will determine whether to stop study participation for that individual.
- If the first 10 subjects experience an AE, the study will stop. This decision will be made under the direction of the IRB in consultation with the DSMB as described below in section 19.2 Data Safety Monitoring.

Risks to subjects from Soybean Oil Placebo:
The placebo is made from soybean oil. There is an allergy risk associated with ingesting soy. The study eligibility criteria excludes any person with a soy allergy.

Risks Associated with Washout:
There are no known risks associated with washout from omega-3 supplement or the soybean oil placebo.

16.0 Potential Benefits to Subjects

Subjects in the omega-3 supplement arm will receive the investigational product at no cost. (Those in the placebo arm will receive placebo at no cost.). Participants will also receive two free blood spot tests measuring omega-3 levels: one at baseline, and one at the end of the 12 weeks of the study.

Overall, the potential benefits to society of this feasibility study is to determine if a larger study on omega-3 supplementation for recovery of Long Covid Syndrome is warranted.

17.0 Data Management and Confidentiality

17.1 Data analysis plan

All study data will be summarized with descriptive statistics. Continuous variables will be summarized with means, standard deviations, medians and ranges. Categorical variables will be summarized with counts and percentages. Data will be summarized overall and separately by the two study arms: Omega-3 supplement or placebo. In general, continuous endpoints will be compared between groups using t-tests or Wilcoxon rank sum tests, as appropriate. Categorical endpoints will be compared between groups using chi-square tests or Fisher's exact tests, as appropriate.

The primary analysis will be the comparison of groups on the long covid-19 symptoms recovery using a chi-square test or Fisher's exact test, as appropriate.

Additional exploratory analyses may be conducted to better understand relationships within the data.

Results with a p-value less than or equal to 0.05 will be considered statistically significant. No adjustments for multiple comparisons will be implemented as this is a feasibility study not statistically powered for analyses.

17.2 Steps to secure the data during storage, use, and transmission

Participants' identifying information will be kept separate from their demographic questionnaire and their other surveys for this study within REDCap. Participants' responses and objective data will be linked to identifying information only through a unique identifier and the information used to link records with identifying information will be kept in a securely locked file cabinet only accessible to the study team. Electronic data will be stored in password protected databases on the secure Hackensack Meridian Health server. Identifying information will not be included on datasets used for statistical analysis and study progress reports.

17.3 Information included in that data or associated with the specimens

No specimens will be stored as part of this study. The only specimens collected will be the two spot blood samples which will be sent to OmegaQuant lab. The data will include variables describing participants' survey responses, and any notes in REDCap from 12 weekly check-in calls from the RC.

For the two spot blood sample tests for each subject, the specimens will be coded before being sent to OmegaQuant Lab, associated with University of South Dakota Medical Center. This lab will only receive de-identified samples, and no identifying patient information.

- *Mode of data storage.*

  Data collected from questionnaires will be stored on the REDCap database on the HMH server. Any paper files will be stored on site at HUMC in locked file cabinets only accessible by the study staff.

- *Duration of data storage.*

  Data will be stored for 6 years after the end of the study, per HMH requirements.

- *Access to data.*

  Access to the data will be restricted to the study staff.

- *Responsibility for receipt or transmission of the data.*

  The PI will be responsible for receipt and transmission of the data.

- *Transportation of the data.*

  The data should not need to be transported. However, if there is a need to transport the data, secure file transfer will be used.

- *Type of data being collected, stored, transmitted and shared.*
  - Protected Health Information (PHI)

- Personally Identifiable Information (PII)

● All computer software to protect against malware will be kept up-to-date and operational. All operating system and software updates and patches will be applied regularly.

● Codes linking participants' identifying information with de-identified data will be stored separately from the corresponding data sets.

● The data will only be accessed on HMH workstations and laptops such that encryption and password protection will be in place with two-factor authentication required for access.

● Access to the data is limited to the study team. Any study staff added to the project will be approved by the PI and added to the IRB protocol.

All HMH policies and procedures for data collection, storage, transmission and destruction will be followed.

18.0 Informed Consent Process

Obtaining consent:

● The consent process will take place online via REDCap.

● No waiting period is required between informing prospective participants and obtaining consent.

● The study will follow the informed consent process for research.

Process to Document Consent in Writing

- The study will document participants' informed consent in writing (electronically) via REDCap.
- The consent document will be attached to the IRB submission.

19.0 Adverse Event Reporting and Monitoring

Clinical criteria for withdrawing an individual subject: Subjects may call the PI at the phone number listed on the consent form at any time to report any concerns which may or may not warrant withdrawal from the study. Additionally, the subject will receive a check-in call 1x per week to discuss any issues of concern. The study physicians, Dr. Sarkar and Dr. Parulekar, will be informed of any issues that arise which may or may not warrant a subject being removed from the study due to safety or toxicity concerns.

19.1 Adverse Events

19.1.1 Definitions

Unanticipated problems involving risk to participants or others: Any incident, experience, outcome, or new information that:

1. Is unexpected; and

2. Is related or possibly related to participation in the research; and

3. Indicates that subjects or others are at a greater risk of harm (including physical,

psychological, economic, legal or social harm) than was previously known or recognized.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Serious adverse event (SAE): Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.

19.1.2 Reporting of AEs/SAEs

AE will be reported and recorded from the time of the first dose of study drug through 30 days after the last dose of study drug. AE monitoring should be continued for at least 30 days following the last dose of study supplement. AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE. The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last visit. AEs may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments. An AE should be followed and an assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

It is the responsibility of the PI (and/or sub-investigators) to report all unanticipated problems involving risks to subjects or others to HMH IRB.

For unanticipated problems/adverse events associated with clinical trials that do not meet the criteria in Section 19.1.1, the investigator or study team member should describe the events at the time of continuing review.

19.2 Data Safety Monitoring

The Hackensack Meridian Health Data and Safety Monitoring Board (DSMB) will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated feasibility study utilizing a non-FDA approved supplement for which the PI holds the IND it is considered a moderate risk study which requires real-time monitoring by the PI and study team and reviewed monthly by the HMH DSMB.

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution-based meetings and on monthly teleconferences. All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participants. Progress on the trial will be reviewed by the HMH DSMB monthly from the time the first participant is enrolled on the study. Results of the DSMB meetings will be forwarded to the IRB with recommendations regarding need for study closure. DSMB recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the PI to ensure that the DSMB is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored. A written copy of the DSMB recommendations will be given to the trial PI and the IRB. If the DSMB recommends a study change for participant safety or efficacy reasons, the trial PI must act to implement the change as expeditiously as possible. If a recommendation is made to change a trial for reasons other than patient safety or efficacy, the DSMB will provide an adequate rationale for its decision. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMB.

19.3 End of Study

The End of Study will occur when all participants have completed the 6 month follow-up period (i.e., when the last patient has expired, been followed for 6 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first). At the 6 month point, one of the study physicians or the RC will call the subject with a quick phone survey, captured in REDCap.

20.0 Ethical considerations and Trial Administration

20.1 Institutional Review Board (IRB) Review

The final study protocol, ICF, and surveys including data collection tools will be approved by the Hackensack Meridian Health Institutional Review Board (IRB). Approval will be received in writing before initiation of the study.

Any changes to the study design will be formally documented in protocol amendments and will be approved by the IRB prior to implementation.

20.2 Subject Confidentiality

The patient collected data, and all analysis of the data will adhere to HIPAA & institutional patient confidentiality requirements as described above.

More specifically, a coding system will be used for which a unique identifier (study ID number) will be assigned to each patient name and contact details. Only the study number will be included in the data collection tool, data analysis software and potential publications. The list with the direct identifiers (for the purposes of linking data with the samples and keeping track of patients) will be stored separately in a secure server at each site.

Analytical datasets will be stored on secure servers that also limit access to the investigator team. Should results of the study be published or reported, individual names or other identifying information will not be used.

20.3 Data Storage/Security

All data will be stored on a Hackensack Meridian Health password protected computer only accessible by the investigator team.

Electronic data will be managed using a secure, web-based system that has user-level access control. Analytical datasets will be stored on secure servers that also limit access to the investigator team.

20.4 Retention of Records

Records will be retained in accordance with regulatory, organizational and sponsor requirements, but for no less than six (6) years following the completion of the research. Disposal of records will be done in such a manner that no identifying information can be linked to research data.

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Appendix A: Inclusion / Exclusion Eligibility Survey

Inclusion/Exclusion Eligibility Survey

Please complete the survey below.

Thank you!

1. Are you a team member at Hackensack Meridian Health?	○ Yes ○ No
2. Are you age 18 or over?	○ Yes ○ No
3. Have you tested positive for coronavirus (COVID-19) via PCR test? (Note: home test or other rapid test MUST be confirmed by a PCR test)	○ Yes ○ No
4. On what date were you diagnosed with Covid-19 via PCR test?	_____
5. Have you been experiencing symptom(s) related to covid-19 for more than 12 weeks after initial infection?	○ Yes ○ No
6. Which of the ongoing covid-19 symptoms have you been experiencing? (please check all that apply)	☐ Respiratory symptoms (shortness of breath and/or cough) ☐ Fatigue ☐ Loss of taste ☐ Loss of smell
7. Were any of these symptoms present before your covid-19 infection?	○ Yes ○ No
8. Where you ever hospitalized for covid-19?	○ Yes ○ No
9. Did you require supplemental oxygen for covid-19?	○ Yes ○ No
10. Do you have a known soy allergy?	○ Yes ○ No
11. Do you have a known allergy to fish?	○ Yes ○ No
12. Are you able to take an online survey every other week (bi-weekly) for the study?	○ Yes ○ No
13. Are you able to take your own blood pressure and record it in bi-weekly online survey?	○ Yes ○ No
14. If you qualify, are you willing to participate in this 12-week study and be assigned to either intervention or placebo arm? This means you will be assigned to either take the omega-3 supplement or a placebo (pill with soybean oil in it).	○ Yes ○ No

15. Are you currently taking an omega-3 supplement or other high-dose supplement (over 2,000 IU) with potential for aiding recovery of long covid syndrome (e.g. zinc, Vit C, Elderberry)?	○ Yes ○ No
16. Are you able to take/swallow six mini-pills daily?	○ Yes ○ No ○ I don't know
17. Are you able and willing to give a spot blood sample (2 drops) at the beginning (baseline) and end of the study?	○ Yes ○ No

Appendix B: Demographic/Baseline Survey

Confidential

Demographic / Baseline Survey - Covid Recovery Study

Please complete the survey below.

Thank you!

What is your last name?

_____

Please provide your mailing address so that we can mail your kit of supplies for study participation. Your supplies will arrive by FedEx, in 2 shipments.

_____

What is your first name?

_____

What is your gender?

- ○ Female
- ○ Male
- ○ Unknown

What is your race?

- ☐ Black or African American
- ☐ White
- ☐ Asian
- ☐ American Indian or Alaska Native
- ☐ Other
- ☐ Unknown

(choose multiple if needed)

What is your ethnicity?

- ○ Hispanic
- ○ Non-Hispanic
- ○ Unknown

Other race not listed above

_____

What is your cell phone number? (This will only be used by the study team to reach you.)

_____

What is your work phone number? (This will only be used by the study team to reach you.)

_____

What is your age?

_____

Has any doctor or other health care provider ever told you that you have any of the following illnesses? (please check all that apply)

- ☐ Diabetes or high blood sugar
- ☐ Hypertension or high blood pressure
- ☐ High cholesterol
- ☐ Stroke (ischemic or hemorrhage)
- ☐ Chronic lung disease such as asthma, emphysema, or chronic bronchitis
- ☐ Heart disease
- ☐ Cancer (other than skin cancer)
- ☐ Depression
- ☐ HIV/AIDS
- ☐ COPD
- ☐ Other

If "other" is checked off, please specify.

_____

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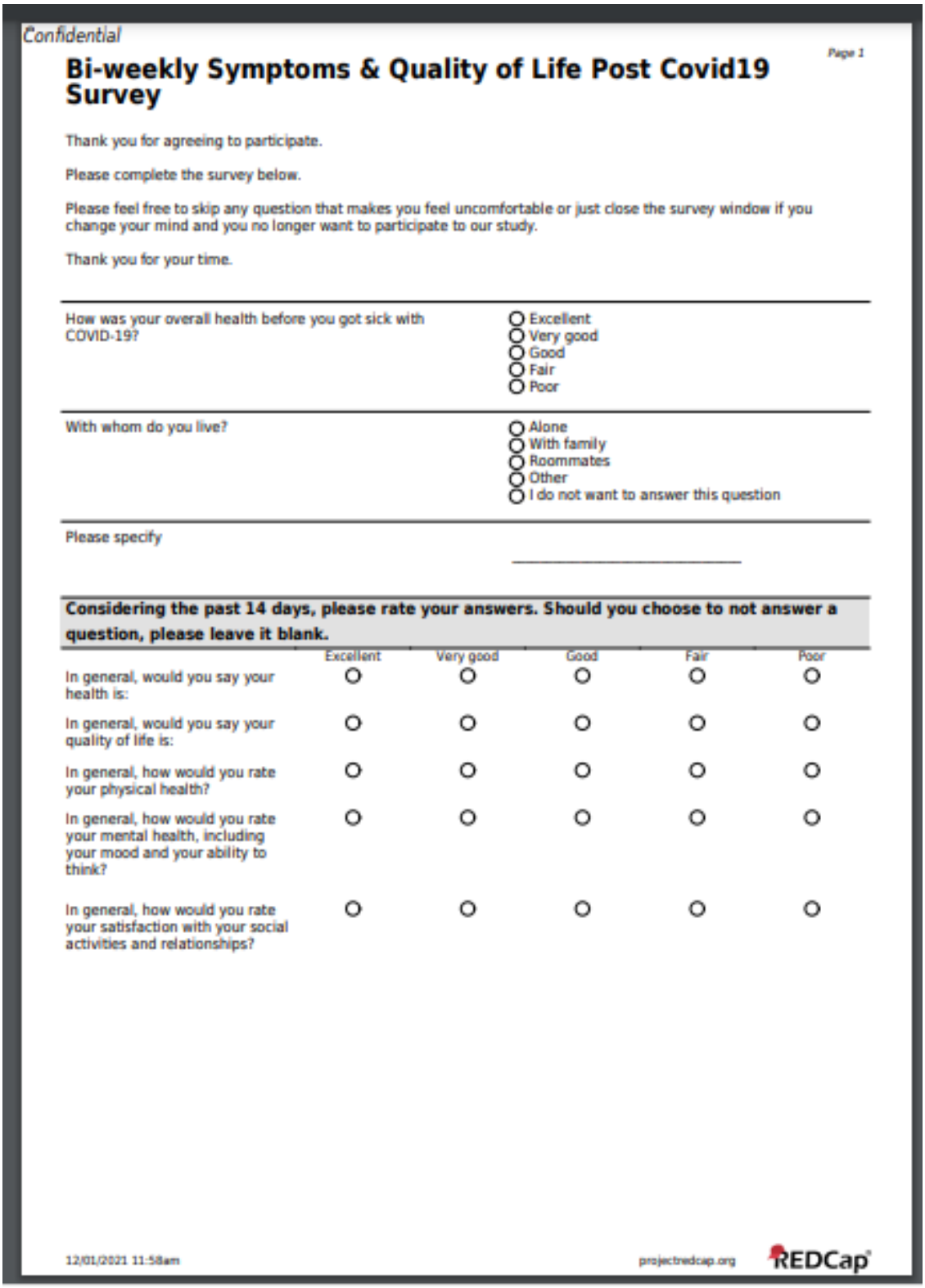
Please list any recent (adult) allergies to food, medicine, herbal or environmental items, with the reactions and dates.	_____
Do you use tobacco products (e.g., cigarettes, cigarillos, e-cigs, cigars)?	◯ Yes, I currently use tobacco products ◯ No, but I used tobacco products in the past ◯ No, I have never used tobacco products
Have you received the covid-19 vaccine?	◯ Yes ◯ No
Are you currently experiencing any side effect(s) from the covid-19 vaccine?	◯ Yes ◯ No
If yes, please describe:	_____

Appendix C: Bi-weekly Symptoms & Quality of Life Post Covid Survey



Confidential

Bi-weekly Symptoms & Quality of Life Post Covid19 Survey

Thank you for agreeing to participate.

Please complete the survey below.

Please feel free to skip any question that makes you feel uncomfortable or just close the survey window if you change your mind and you no longer want to participate to our study.

Thank you for your time.

How was your overall health before you got sick with COVID-19?

- ○ Excellent
- ○ Very good
- ○ Good
- ○ Fair
- ○ Poor

With whom do you live?

- ○ Alone
- ○ With family
- ○ Roommates
- ○ Other
- ○ I do not want to answer this question

Please specify _____

Considering the past 14 days, please rate your answers. Should you choose to not answer a question, please leave it blank.

	Excellent	Very good	Good	Fair	Poor
In general, would you say your health is:	○	○	○	○	○
In general, would you say your quality of life is:	○	○	○	○	○
In general, how would you rate your physical health?	○	○	○	○	○
In general, how would you rate your mental health, including your mood and your ability to think?	○	○	○	○	○
In general, how would you rate your satisfaction with your social activities and relationships?	○	○	○	○	○

In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	○	○	○	○	○

To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

- ○ Completely
- ○ Mostly
- ○ Moderately
- ○ A little
- ○ Not at all

How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?

- ○ Always
- ○ Often
- ○ Sometimes
- ○ Rarely
- ○ Never

How would you rate your fatigue on average?

- ○ Very Severe
- ○ Severe
- ○ Moderate
- ○ Mild
- ○ None

Considering the past 14 days, please rate the amount of difficulty you had when doing the following activities. Should you choose not to answer a questions, please leave it blank.

	No difficulty	A little difficulty	Some difficulty	Much difficulty	I did not do this in the past 7 days
Dressing yourself without help	○	○	○	○	○
Walking 50 steps/paces on flat ground at a normal speed without stopping	○	○	○	○	○
Walking up 20 stairs (2 flights) without stopping	○	○	○	○	○
Preparing meals	○	○	○	○	○
Washing dishes	○	○	○	○	○
Sweeping or mopping	○	○	○	○	○
Making a bed	○	○	○	○	○
Lifting something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries)	○	○	○	○	○

Carrying something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries) from one room to another	○	○	○	○	○
Walking (faster than your usual speed) for ½ mile (almost 1 km) without stopping	○	○	○	○	○

Please select which week you stopped experiencing the symptoms described below.
If you never experienced this symptom, please select N/A

	During the first two weeks since my covid-19 diagnosis	During the third week since my covid-19 diagnosis	During the fourth week since my covid-19 diagnosis	I still experience this symptom	N/A - I never experienced this symptom
Shortness of breath	○	○	○	○	○
Cough	○	○	○	○	○
Fatigue	○	○	○	○	○
Lack of taste	○	○	○	○	○
Lack of smell	○	○	○	○	○
Other	○	○	○	○	○

If you answered "Other," please specify/describe additional symptom #1: _____

If you answered "Other," please specify/describe additional symptom #2: _____

If you answered "Other," please specify/describe additional symptom #3: _____

Comment - Optional (please add here anything else you might want to share with us regarding any symptoms and/or your quality of life since your covid-19 diagnosis) _____

Please write-in your blood pressure, taken anytime in the last 2 weeks: _____

Source of blood pressure (BP) equipment and method:

○ BP was taken by machine at home
○ BP was taken by machine at a pharmacy
○ BP was taken manually in medical office

Appendix D: Follow-up Feasibility Survey & Study Discontinuation Verification

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Follow-up Survey - Covid Recovery Study

Please complete the survey below.

Thank you!

Were the instructions on how to take the pills clear?	○ Yes ○ No ○ Neutral / I don't know
If no, why not?	_____
Did you not take the pills (skip one or more doses) at any time during 12-week study? (please refer to your pill log calendar)	○ No ○ Yes
If yes, how often did you not take the pills?	_____
For how many days in a typical week did you take the pills?	_____
Please include any comments about missed doses here:	_____
Were the pills easy to take?	○ Yes ○ No ○ Neutral / I don't know
If no, why not?	_____
Did taking the pills interfere with your daily activities somehow?	○ Yes ○ No ○ Neutral / I don't know
If yes, how?	_____
How satisfied were you with your experience taking the pills?	○ Very satisfied ○ Satisfied ○ Neutral ○ Dissatisfied ○ Very dissatisfied
Are you willing to be contacted in the future about opportunities to participate in other research studies?	○ Yes ○ No

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Since starting your participation in this study, has any doctor or other health care provider told you that you have any of the following illnesses? (please check all that apply)	☐ Diabetes or high blood sugar ☐ Hypertension or high blood pressure ☐ High cholesterol ☐ Stroke (ischemic or hemorrhage) ☐ Chronic lung disease such as asthma, emphysema, or chronic bronchitis ☐ Heart disease ☐ Cancer (other than skin cancer) ☐ Depression ☐ HIV/AIDS ☐ Other
If you answered "Other," please specify:	_____
Please share anything else you would like us to know about your experience participating in this study:	_____
During the 12-week study, did you receive the covid-19 vaccine?	○ Yes ○ No
If you did receive the covid-19 vaccine, did you experience any side effect(s)?	_____
For how long did you experience side effect(s)? (please specify in # of days)	_____
Is there anything else you would like to tell us that you might be important that we did not ask about?	_____

Study Discontinuation Verification

Please complete the survey.

Thank you!

1) Have you discontinued study participation?
- ○ Yes
- ○ No

2) How many pills altogether do you have in your bottle(s) of supplement/placebo?

_____

3) Please discard all of the study supplement/placebo pills that you have, and indicate that here. Have you discarded your study supplement/placebo?
- ○ Yes
- ○ No

Appendix E: Omega-3 Supplement & Labeling Information

KD Nutra™
a KD Pharma Group Company
14193 SW 119 Ave., Miami, FL 33186
www.kdnutra.com

CERTIFICATE OF ANALYSIS

Product Number:	MSU1286	Batch No:	2011090
Product Description:	Oceanblue® MiniCap® Placebo Formula	Manufactured Date:	November 24, 2020
Customer:	Oceanblue LLC.	Test Date:	
Customer Item No.:	N/A		

Tests	Acceptance Criteria	Method	Results
Description	Clear transparent oval soft capsule containing pale yellow oil	STM001	Complies
Fill Weight	458 mg ±5%	USP <2091>	452 mg
Weight Variation	Meets USP <2091>	USP <2091>	Complies
Average Total Weight	647 mg ±10%	USP <2091>	645 mg
Rupture Test	Max. 15 Minutes	USP <2040>	1 minute
Total Aerobic Bacterial Count	<1,000 cfu/g	USP or equivalent	<1,000 cfu/g
Total Mold/Yeast Count	<100 cfu/g	USP or equivalent	<100 cfu/g
Enterobacteriaceae	<100 cfu/g	USP or equivalent	<100 cfu/g
Escherichia coli	Negative/10 g	USP or equivalent	Negative/10 g
Salmonella spp.	Negative/10 g	USP or equivalent	Negative/10 g
Staphylococcus aureus	Negative/10 g	USP or equivalent	Negative/10 g

Tooling Size:	7.5 Oval
Ingredients	Soybean Oil; Gelatin, Bovine; Glycerin; Purified Water; D-Limonene; Ethyl Vanillin.
Allergens:	None*
*Contains highly refined soybean oil. Labeling exempt per US Food Allergen Labeling and Consumer Protection Act (FALCPA)	

Approvals:

Quality Control: _____ Date: 12-09-20

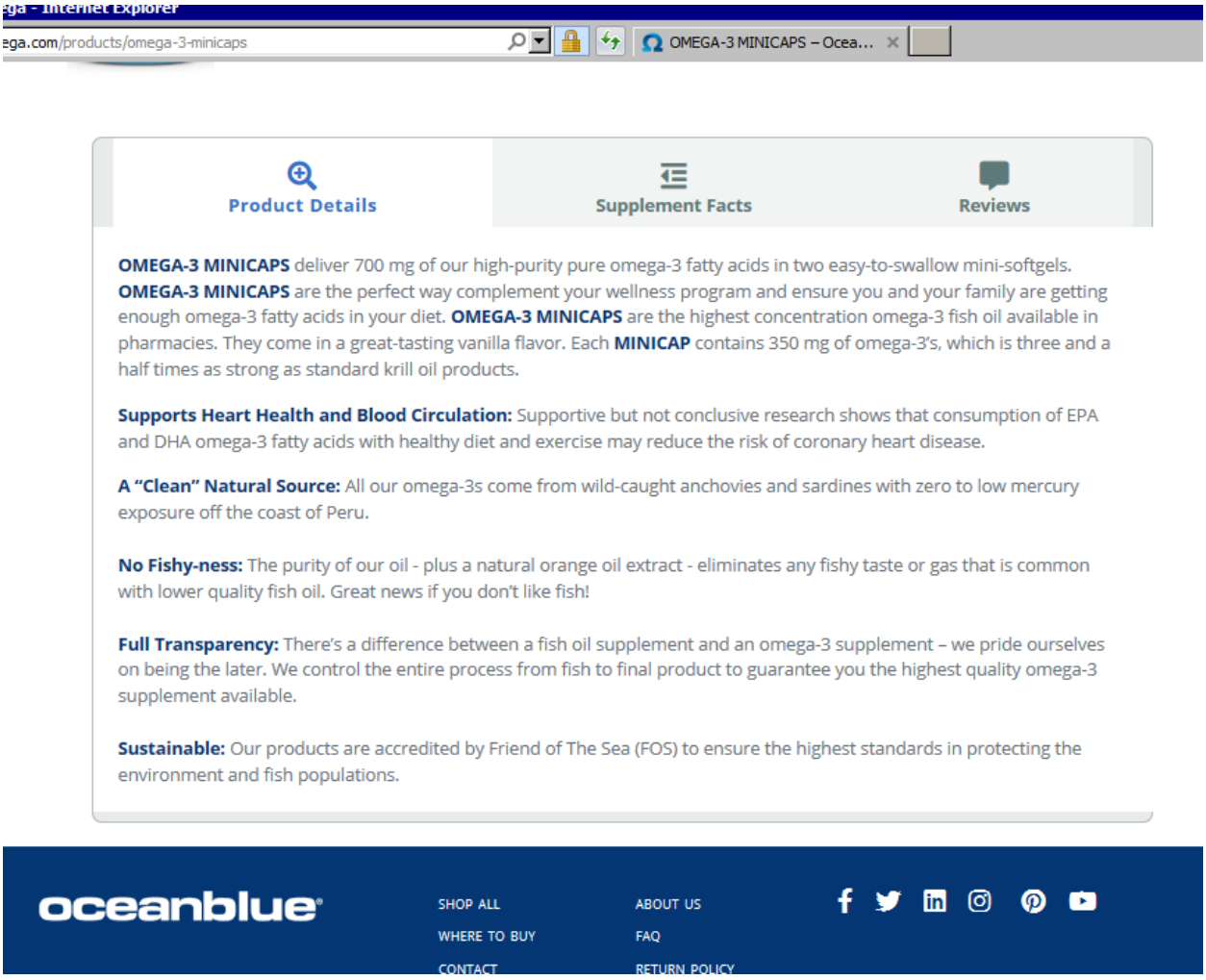
Quality Assurance: _____ Date: 12/10/20

Labeling: There will be only ONE label for both the placebo and IP, to keep the blind.

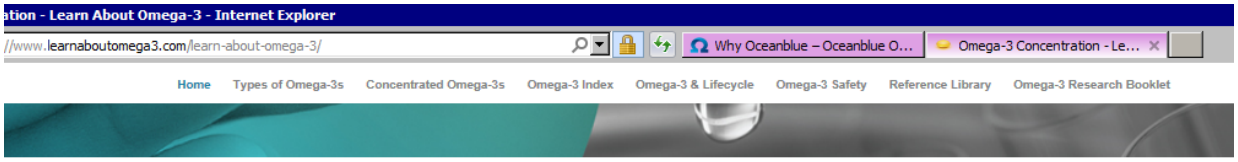
Investigational drug / Placebo label (below is the minimum that will be included)

- Subject ID#
- Expiration date (as per sponsor)
    - prescription (serial) number.
    - date of each dispensing.
    - subject's name.
    - directions for use.
    - name and strength of the drug product (or active ingredient(s) in a compounded prescription) --------> inv. IP name / Placebo
    - prescriber's name.
    - Initials of dispensing pharmacist.

Keep at Room Temperature between 59-86 ºF
Caution: New Drug Limited by Federal (or U.S.) law to Investigational Use.


ega.com/products/omega-3-minicaps
OMEGA-3 MINICAPS – Ocea...
Product Details
Supplement Facts
Reviews
OMEGA-3 MINICAPS deliver 700 mg of our high-purity pure omega-3 fatty acids in two easy-to-swallow mini-softgels. OMEGA-3 MINICAPS are the perfect way complement your wellness program and ensure you and your family are getting enough omega-3 fatty acids in your diet. OMEGA-3 MINICAPS are the highest concentration omega-3 fish oil available in pharmacies. They come in a great-tasting vanilla flavor. Each MINICAP contains 350 mg of omega-3's, which is three and a half times as strong as standard krill oil products.
Supports Heart Health and Blood Circulation: Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids with healthy diet and exercise may reduce the risk of coronary heart disease.
A "Clean" Natural Source: All our omega-3s come from wild-caught anchovies and sardines with zero to low mercury exposure off the coast of Peru.
No Fishy-ness: The purity of our oil - plus a natural orange oil extract - eliminates any fishy taste or gas that is common with lower quality fish oil. Great news if you don't like fish!
Full Transparency: There's a difference between a fish oil supplement and an omega-3 supplement – we pride ourselves on being the later. We control the entire process from fish to final product to guarantee you the highest quality omega-3 supplement available.
Sustainable: Our products are accredited by Friend of The Sea (FOS) to ensure the highest standards in protecting the environment and fish populations.
oceanblue
SHOP ALL
WHERE TO BUY
CONTACT
ABOUT US
FAQ
RETURN POLICY


Omega - Internet Explorer
eanblueomega.com/pages/why-oceanblue
Why Oceanblue – Oceanblue…
THE OCEANBLUE DIFFERENCE
PURITY
More benefits. Less fat.
At Oceanblue, we create omega-3 supplements ... not run-of-the-mill fish oil supplements. What's the difference?
First our omega-3 oils are refined in Norway and then further concentrated in our state-of-the-art facility in Germany.
During this process, we remove unhealthy fats, impurities and by-products to create high-purity, concentrated omega-3 products.
Click here to learn more about why purity and concentration matters when choosing an omega-3 supplement.
POTENCY
What you need in fewer softgels.
When choosing an omega-3 supplement there are two important things to consider:
What is the amount of omega3s in a serving?
How many softgels make up a serving?
Depending on goals, you may need 500 mg to over 1,000 mg of omega-3s per day to see health benefits.
Being able to reach that daily dose in as few softgels as possible is critical to remaining committed to a supplement program.
Click here to learn more about why potency of omega-3s per serving is so important.
3T'S OF OCEANBLUE
Transparency, Traceability, and Technology.
At Oceanblue, we control the entire process of creating our products from fish to final packaging.
This allows us to provide transparency of all our ingredients and manufacturing processes as well as the ability to trace back our omega-3 oils to their source.
Since omega-3s are all that we do – and we do it well – you can trust our expertise to give you and your family the best products available.
Click here to learn more about how Oceanblue products get from our family to yours.



INTRO TO HIGH-CONCENTRATION / HIGH-POTENCY OILS

Omega-3 fatty acids are among the most widely researched nutrients in the world; however, consumer confusion persists surrounding the benefits of omega-3, and which factors are important when they shop for an omega-3 supplement.

There are two primary factors consumers should consider:

1 **Fish oil does not equal omega-3:**

what benefits individual health is their omega-3 status and reaching sufficient levels often requires high dosages of omega-3 – not to be confused with the amount of fish oil. It is important to read the label on fish oils to see how much omega-3 they deliver.

2 **Consistency and longevity are key:**

individuals can expect to see improved omega-3 levels – and improved health outcomes – after months of daily, consistent supplementation. For long-term health and wellness, individuals need a habit they can sustain long-term.

Therefore, supplementation with high-concentration – or high-dosage – omega-3 oils present the best option for consumers to consistently increase their daily omega-3 intake. High-concentration omega-3s allow for higher dosage of omega-3 in fewer (or smaller) capsules, which in turn leads to easier, and sustained consumption.