BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057024
Article Type:	Protocol
Date Submitted by the Author:	02-Sep-2021
Complete List of Authors:	Legacy, Mark; Patterson Institute for Integrative Oncology Research, Research; Ottawa Hospital Research Institute, Clinical Epidemiology Program Conte, Ellen; Patterson Institute for Integrative Oncology Research, Research Psihogios, Athanasios; Patterson Institute for Integrative Oncology Research, Research Ramsay, Tim; Ottawa Hospital Research Institute, CEP Fergusson, Dean; Ottawa Hospital Research Institute, Clinical Epidemiology Kanji, Salmaan; The Ottawa Hospital, Department of Pharmacy; Ottawa Hospital Research Institute, Clinical Epidemiology Program Simmons, John-Graydon; Ottawa Hospital Research Institute, Clinical Epidemiology Program Wilson, Kumanan; Ottawa Hospital Research Institute, Clinical Epidemiology Program Seely, Dugald; Patterson Institute for Integrative Oncology Research, Research; Ottawa Hospital Research Institute Clinical Epidemiology Program
Keywords:	COMPLEMENTARY MEDICINE, COVID-19, Clinical trials < THERAPEUTICS

Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

Mark Legacy, BSc[1,2], Dugald Seely, ND, MSc[1,2] ND, MSc, Ellen Conte, ND[2], Athanasios Psihogios, ND (Inactive)[2], Tim Ramsay, PhD[1], Dean A. Fergusson, PhD[1], Salmaan Kanji, BSc, PharmD[1,4], John-Graydon Simmons, MD[1], Kumanan Wilson, MD[1]

1 – Ottawa Hospital Research Institute, Ottawa ON, Canada; 2 – Patterson Institute for Integrative Oncology Research, Toronto, ON, Canada; 3 – The Centre for Health Innovation, Ottawa, ON, Canada; 4 – The Ottawa Hospital Department of Pharmacy, Ottawa ON, Canada

Corresponding Author:

Mark Legacy, BSc

Clinical Research Coordinator – Integrative Oncology

The Ottawa Hospital Research Institute & The Patterson Institute for Integrative Oncology Research

429 MacLaren Street, Ottawa ON K2P 0M7

613-792-1222 ext. 1

mlegacy@thechi.ca

Key Terms

Complementary medicine, COVID-19, clinical trial, dietary supplements, integrative medicine, natural health products, vitamin C, vitamin D, vitamin K2, zinc

Word Count: 3988

Abstract

Introduction

Coronavirus Disease 2019 (COVID-19) has caused morbidity, hospitalizations, and deaths worldwide. Despite four approved vaccines for COVID-19 in Canada, there is still a need for effective treatments, especially for people in the community. Vaccine efficacy is not 100% and long-term efficacy is still unknown. Furthermore, there are challenges to herd immunity including vaccine hesitancy and underlying conditions preventing vaccination. We aim to explore if the nutrients vitamin C, vitamin D, vitamin K2, and zinc are an effective treatment option for outpatients diagnosed with COVID-19. The primary outcome is the difference in participant-reported overall health; secondary outcomes include the effect on health status, symptom severity and duration, frequency and length of hospitalizations, and mortality.

Methods and Analysis

This study is a two-arm, parallel group, double-blind, placebo-controlled, phase III randomized controlled trial. 200 patients will be recruited remotely from COVID-19 test centres in Ottawa, Canada associated with The Ottawa Hospital. Overall health will be measured using the EuroQol Visual Assessment Scale; health status will be measured using the EuroQol 5-dimension 5-level

questionnaire; symptom severity and duration will be measured using an independently developed questionnaire; analyses will use an area under the curve approach and compare mean scores using unadjusted t tests. Study data will be recorded on electronic case report forms using the Research Electronic Data Capture platform. An independent data safety and monitoring board will perform ongoing review of the study for feasibility and safety.

Ethics and Dissemination

This study has received ethical approval from the research ethics boards of the Canadian College of Naturopathic Medicine and the Ottawa Health Sciences Network, as well as regulatory approval from the Therapeutic Products Directorate and Natural and Non-Prescription Health Products Directorate of Health Canada. Results will be published in a peer-reviewed scientific journal with open access.

Registration

This study is registered at https://clinicaltrials.gov: NCT04780061

Article Summary

Strengths and Limitations

- Blinding, randomization, and placebo control enhance the trial's validity.
- Large spectrum of outcomes allows for both rigorous and exploratory analyses.
- The study procedures regarding remote screening, recruitment, follow-up, and product dispensation are novel in this field and will act as a framework for future research.
- Virtual nature of the study and necessity for internet literacy may create selection bias.

- Variable length of time from symptom onset to treatment commencement due to delays in result reporting may reduce the effectiveness of the investigational product.

Introduction

Background and Rationale

Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused hospitalizations, morbidity, and deaths worldwide. COVID-19 causes mild to moderate flu-like symptoms in most people, and can cause severe disease including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death particularly in high-risk individuals.[1] As of June 2021, over 177 million people have been diagnosed with COVID-19 and over 3.8 million deaths have occurred as a result of infection.[2]

There are currently four approved COVID-19 vaccines in Canada.[3] Despite this, effective treatments are still needed. None of the four vaccines are 100% effective, and long-term immunity is yet to be determined.[4] In addition, there are challenges to achieving herd immunity based on an inability for those with certain underlying conditions to be vaccinated and vaccine hesitancy.[5] Treatments for COVID-19 are currently limited. In Canada, the only approved treatments are Remdesivir and the monoclonal antibodies Bamlanivimab, Casirivimab, and Imdevimab.[6] Remdesivir is indicated for COVID-19 positive patients with pneumonia needing supplemental oxygen; however, results from trials are mixed.[7,8] The three monoclonal antibodies are indicated for people with mild to moderate COVID-19 who are at high risk for progressing to hospitalization or death.[9,10] All three monoclonal antibody treatments are permitted under an interim authorization pending the results of clinical trials to verify their clinical benefit. To date, there are no fully approved treatments for non-hospitalized patients diagnosed with COVID-19.

The use of natural health products (NHPs), including vitamins, minerals, and herbs, to treat COVID-19 infections has received both academic and public attention.[11,12] Various NHPs have undergone observational and clinical research for a wide variety of other upper respiratory tract infections (URTIs). These trials have mainly focused on the treatment of URTI symptoms, including reducing the duration and severity of the illness. Some of the most heavily researched NHPs include andrographis,[13,14] quercetin,[15] vitamin C,[16-18] vitamin D,[19-21] and zinc.[22] At the time of the creation of this protocol (January 2021), there was observational evidence to support some NHPs for the treatment of COVID-19, such as vitamin D[23,24] and vitamin K;[25] however, there were no published double-blind, placebo-controlled, randomized clinical trials studying NHPs and COVID-19 symptoms.

A more recent review of the literature revealed the presence of new COVID-19-specific NHP research. A June 2021 meta-analysis of ten observational studies and three randomized controlled trials (RCT) (n = 2933) reported that supplementation with vitamin D significantly reduced ICU admissions and mortality, while reducing the risk of adverse outcomes, exclusively when administered after a COVID-19 diagnosis.[26] One RCT applying similar interventions as our protocol (8,000 mg ascorbic acid and 50 mg zinc gluconate) found a non-statistically significant benefit for each supplement on their own, and in combination, compared to standard care.[27] Of note, the study was terminated early due to being underpowered because of recruiting less than half of the intended sample size, and experienced considerable compliance issues.

Based on the above studies for COVID-19 and other similar URTIs, the nutrients vitamin C, vitamin D3, vitamin K2, and zinc stood out as the most promising NHPs for the treatment of symptoms caused by COVID-19, and thus were chosen as interventions for this study.

Choice of Comparator

The comparator in this trial will be a placebo. Currently, there are no standard of care treatments for people in the community diagnosed with COVID-19; thus, a placebo offers the most rigorous assessment of efficacy while having no detriment to safety due to lack of standard treatments. Should a participant be hospitalized, they will be asked to stop all study activities, including taking investigational product, until they are back home and able to tolerate the intervention again. If hospital-initiated treatments continue while at home, these will take priority over the study intervention if there is a safety concern identified by the qualified investigator or treating physician. As the investigational products in this study are readily available over the counter, monitoring for contamination and cross-over is imperative. This will be accomplished through weekly follow-up with all participants.

Objectives

We hypothesize that supplementation with vitamin D3, vitamin C, vitamin K2, and zinc will increase participant-reported overall health in outpatients diagnosed with COVID-19 compared to a placebo by reducing the severity and duration of common COVID-19 symptoms experienced in a community setting.

The primary objective of this study is the difference in participant-reported overall health between arms; secondary objectives include:

1. Effect of the intervention on the health status of participants

2. Symptom severity including self-reported measures for fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, shakes/chills, congestion, and loss of taste and smell
3. Total symptom duration
4. Incidence of delayed return to usual health
5. Frequency of hospitalizations, including emergency room (ER) visits, acute care admissions, and intensive care unit (ICU) admissions
6. Hospital length of stay (if applicable)
7. All-cause mortality

Study Design

This study is a two-arm, parallel group, double-blind, placebo-controlled, phase III trial powered to detect meaningful differences in the overall health of adults with COVID-19 between the treatment and control arms at 21 days. Total trial duration for participants is 12 weeks, and the treatment period runs for 21 days following randomization.

Participants, Interventions, and Outcomes

Study Setting

This study will recruit outpatients from Ottawa, Canada from COVID-19 test centres in the community associated with The Ottawa Hospital (TOH). The primary site of study conduct will be the Centre for Health Innovation (CHI), an integrative care clinic located in Ottawa. All recruitment, study activities, and follow-up will take place remotely as participants will be in quarantine for at least 14 days. Study staff will only communicate with participants by phone or email, and participants will complete all study activities in their own homes.

Eligibility Criteria

To be eligible for this study, patients must meet the following inclusion criteria:

1. Adults (≥18) who test positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) in an outpatient setting
2. Access to internet

The criterion of access to internet may cause selection bias in our population and will not be entirely representative of COVID-19-positive patients in the Ottawa community; however, due to the nature of the study, the progression of the disease, and the public health recommendations to maintain both safety of participants and research staff, in-person consent and follow-up is not feasible.

In addition, patients must not exhibit any of the following exclusion criteria:

1. Symptom onset greater than 4 days prior to enrolment
2. Regular supplementation with >500 mg vitamin C, >1000 units vitamin D (any form), >120 mcg vitamin K (any form), or >15 mg zinc taken daily within the past month
3. Currently taking warfarin or an equivalent vitamin K antagonist anticoagulant
4. End stage chronic kidney disease
5. History of calcium oxalate kidney stones
6. Active granulomatosis (sarcoidosis, tuberculosis, lymphoma)
7. Known hypercalcemia or hypervitaminosis D
8. Currently taking either of the following antibiotics: cephalexin, tetracyclines
9. Known allergy to any investigational product, silicon dioxide, cellulose, or medium chain triglyceride oil

10. Participating in an investigational study or participation in an investigational study within the past 30 days

The first exclusion criterion was chosen in an attempt to include patients who have the best chance at a potential benefit from the intervention. The median time to symptom resolution for COVID-19 patients has been reported to be 4-8 days;[28] therefore, recruitment of patients whose symptom onset date was 5 or more days before enrolment would likely yield a large proportion of patients whose symptoms have already resolved. The second exclusion criterion balances feasibility with contamination. Those supplementing with one or more of the investigational products could introduce bias to the population and skew results; however, low-dose supplementation is common amongst Canadians and would severely hinder recruitment.

Interventions

The interventions for this study will be vitamin C, vitamin D3, vitamin K2, and zinc plus equivalent placebos. All investigational products will be manufactured by New Roots Herbal under the brand name Vitazan Professional. Specific formulations of each investigational product are as follows:

Study Product #1: Vitamin D3 50,000 IU

Formulation: Capsule. Each capsule contains 500 mg (50,000 units) cholecalciferol (vitamin D3)

Dose: One capsule on day 1 of the intervention period

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis

Study Product #2: Vitamin K2/D3 Liquid

Formulation: Liquid. Each 0.0285 mL drop contains 30 mcg menaquinone-7 (MK-7, vitamin K2) and 3.125 mcg (125 units) cholecalciferol.

Dose: 0.114 mL (four drops) twice daily for 21 days totalling 240 mcg MK-7 and 1,000 units cholecalciferol per day.

Placebo Equivalent: Medium chain triglyceride oil

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis; warfarin or another vitamin K antagonist anticoagulant

Study Product #3: Vitamin C/Zinc acetate

Formulation: Capsule. Each capsule contains 666 mg ascorbic acid (vitamin C) and 8.3 mg zinc acetate

Dose: Three capsules three times daily for 21 days totalling 6 g ascorbic acid and 75 mg zinc acetate per day.

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: calcium oxalate kidney stones, end stage chronic kidney disease, cephalexin, tetracycline antibiotics

Modifications to the intervention schedule are permitted under the discretion of the qualified investigator (KW) or sub-investigator delegated the task. Adherence to the protocol will be participant-reported through a phone call at the end of the intervention period. Participants will be asked to conduct pill counts for the two capsule-based products and estimate how many doses they have missed of the liquid product.

Absolute contraindications to the investigational products are outlined above and in the exclusion criteria. Should a participant be placed on one of these medications or be diagnosed with one of the conditions, they will stop taking the study product. There are no rescue medications for this study.

Outcomes, Timeline, and Schedule of Events

The full schedule of events is presented in table 1. The primary outcome of this study is the difference in mean participant-reported overall health over 21 days between arms measured using the EuroQol Visual Assessment Scale (EQ-VAS).[29] The EQ-VAS records the respondent's overall current health on a vertical scale between 0 and 100, where the end points are labelled "the best health you can imagine" (i.e., a score of 100) and "the worst health you can imagine" (i.e., a score of 0). The EQ-VAS will be filled out each day while on the intervention (21 days total). The secondary outcomes are as follows:

Health Status: Measured by combining one level from each of the five dimensions of the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire[29] to form a unique health state. The EQ-5D-5L questionnaire will be filled in at baseline and weeks 1, 2, 3, 4, 8, and 12. Mean health state at each time point will be compared between arms.

Symptom Severity & Duration: Measured using an internally-developed questionnaire specific for the most common COVID-19 symptoms, which include: fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, chills, altered taste, altered smell, and nasal congestion.[28,30] Each symptom will be rated on a 4-point severity scale: 0-none, 1-slight, 2-moderate, and 3-severe. Participants will fill in this questionnaire daily while receiving

treatment (i.e., for 21 days). We will compare the total mean symptom scores over 21 days between arms.

Incidence of delayed return to usual health: Measured through follow-up calls with participants at weeks 4, 8, and 12 following randomization. Those experiencing prolonged COVID-19 symptoms lasting 4-12 weeks will be classified as having "ongoing symptomatic COVID-19," while those still afflicted at 12 weeks will be classified as having "post-COVID-19-syndrome."[31] We will compare the number of participants in each arm who exhibit ongoing symptomatic COVID-19 and post-COVID-19 syndrome.

Hospitalization: the rate and type of hospitalization, as well as the length of stay, will be collected from participant medical records where possible and will otherwise be participant-reported. Information will be collected throughout the 12-week study period.

All-Cause Mortality: date of death will be collected through medical records and obituary searches when medical records are not available. Information will be collected throughout the 12-week study period.

Overall health was chosen as the primary outcome as it uses a validated tool and is easily interpretable. Although research on other URTIs focuses heavily on symptom severity questionnaires, currently there are no validated tools for assessing COVID-19 symptom severity. The clinical significance of symptom severity in a non-validated tool is much more difficult to analyze and open to differing interpretations.

The symptom questionnaire developed by our team is largely based on recommendations from the US Food and Drug Administration guidance document for investigators conducting community

clinical trials for COVID-19 prevention or treatment[32] and commonly reported COVID-19 symptoms in both the hospital and community setting.[28,30]

Sample Size

With respect to the primary outcome of participant-reported overall health, power calculations were conducted based on between-group differences and Cohen's guideline for a small effect size of 0.3. A sample size of 176 (88 per arm) provides 80% power to detect a difference at an alpha of 0.05. To account for an approximate 10-15% loss to follow-up we will enrol 200 participants (100 per arm).

Recruitment

Screening for potential participants will be facilitated by clinical staff at COVID-19 test centres in Ottawa associated with TOH. Staff at these test centres are responsible for contacting any person who tests positive for COVID-19. The clinical team will use this opportunity to obtain the patient's consent to be contacted by the research team. Nursing staff will notify the trial coordinator of all patients who agree to be contacted. Study staff at the CHI will then contact each patient by phone and further determine their eligibility. If a patient is interested and eligible, they will be taken through the informed consent process and sign an electronic informed consent form using Adobe Sign.

Over time, the COVID-19 case count in Ottawa has varied greatly. With vaccine distribution continuing to increase, we assume the infection rate will remain steady at 10-15 diagnoses per day; however, not all COVID-19 positive patients will be referred to our group due to competing trials and lack of recruitment from all test centres. We expect to receive referrals for 50% of all people diagnosed with COVID-19. Based on previous trials we have conducted with natural health

products and input from the investigators, we assume 50% of people will be eligible for this study, and 50% of those eligible will be interested in participating. This yields an approximate expected recruitment rate of 1-2 participants per day, and an expected recruitment period of 3-6 months.

Table 1: Schedule of Events

	Time of Assessment										
	Screening (pre-enrolment)	Baseline (Prior to intervention)	Days 1-6	Day 7	Days 8-13	Day 14	Days 15-20	Day 21	Week 4	Week 8	Week 12
Eligibility	✓										
Informed Consent	✓										
Randomization		✓									
Medical History & Current Medications		✓									
Demographics		✓									
Study Intervention			✓	✓	✓	✓	✓	✓			
EQ-VAS			✓	✓	✓	✓	✓	✓			
Symptom Questionnaire			✓	✓	✓	✓	✓	✓			
EQ-5D-5L		✓		✓		✓		✓	✓	✓	✓
Phone Call Follow-Up • Concomitant Medications • Adverse Events • Hospitalizations • Delayed return to usual health				✓		✓		✓	✓	✓	✓

EQ-VAS: EuroQol Visual Assessment Scale; EQ-5D-5L: EuroQol 5-Dimension 5-Level. EQ-VAS and symptom questionnaires must be filled in on the appropriate days. A 3-day window will be allowed for EQ-5D-5L completion and phone call follow-up for the first 4 weeks. The window will increase to 5 days for weeks 8 and 12. Compliance to the intervention will be participant-reported and take place on day 21 or week 4.

Study Methods

Assignment of Interventions

Eligible participants will be randomized using a web-based system developed and maintained by the Ottawa Methods Centre (OMC), an organization that provides consultation services for areas such as research methodology, biostatistics, and data management. Randomization will occur in permuted blocks of 4 and 6 at ratio of 1:1 to one of the following groups: (1) nutrient therapy with vitamin D, vitamin C, vitamin K2, and zinc or (2) placebo. All study staff, treating physicians and participants will be blinded to the allocation. The staff at Vitazan Professional will be the only personnel with knowledge of treatment allocation to facilitate shipment of study product directly to participants. Patients will be randomized once they sign an informed consent form and have their eligibility confirmed by a medical doctor. If un-blinding is deemed to be necessary, the trial coordinator will request the treatment allocation from the OMC or Vitazan Professional.

Data Collection and Management

Study data will be collected on paper case report forms (CRF) or electronic case report forms (eCRF) using the Research Electronic Data Capture (REDCap) platform. All study data, including paper CRFs, eCRFs, and the electronic database, will be managed by the trial coordinator (ML) under the supervision of the principal investigator (DS). Participants will be able to use the REDCap platform to directly enter data or may choose to fill in paper CRFs. To facilitate direct entry to an eCRF, participants will receive an email with a direct link to the eCRF where they can enter their responses. Study data in REDCap will be stored on a secure server located in Toronto, Canada managed by the Canadian College of Naturopathic Medicine. Paper CRFs will be kept at the CHI in locked cabinets.

REDCap has been tested to work on Windows 10, the standard software package at the CHI, as well as Mac OS Catalina and above. As required by Health Canada, the REDCap database has been validated by the study team and is designed to keep track of all users who enter, save, edit, and update data entered to the eCRFs, and to automatically provide a timestamp of all activity. See *Supplementary Materials* section 1.0 for an outline of the data validation plan.

Statistical Methods

All analyses will follow an intention to treat approach. Continuous and quasi-continuous variables (participant-reported health & health status, symptom severity, and length of stay) will be compared between arms using unadjusted t-tests. Dichotomous outcomes (delayed return to usual health, hospitalizations and deaths) will be compared between arms using Chi-square tests or Fisher's exact tests where appropriate. Time to symptom resolution will be displayed graphically with Kaplan-Meier curves and differences between arms will be compared with a log-rank test.

Safety and Data Monitoring

External oversight for this trial will be provided by an independent data safety and monitoring board (DSMB). The DSMB will meet either in-person or remotely to discuss matters related to the safety of study participants, validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol and data completeness. The DSMB will review interim data once 100 participants are enrolled or after 4 months, whichever comes first. The DSMB may choose to review data at other times at their discretion. Based on review of the safety data, the DSMB may recommend continuation of the study without modification(s), study interruption, study termination, or modification(s) of the trial.

Additionally, the trial will have a quality control monitoring process in place to verify that all data are accurate and complete. Investigators will permit trial-related monitoring, audits and regulatory inspections, and direct access to source data/documents. The monitor will generate a site monitoring report for the qualified investigator detailing significant findings, deviations, deficiencies, plausibility, record completeness and any corrective actions required.

Adverse events (AE) will be collected by the study team for each participant throughout the intervention period plus one additional week using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Classic or other symptoms of COVID-19 will not be recorded as AEs. These include fever, new or worsening cough, shortness of breath/difficulty breathing, fatigue, myalgia/arthralgia, sore throat, sputum production, dysphagia, new olfactory or taste disorders, pneumonia, rhinorrhea, chills/shakes, or nasal congestion. Such events are expected in a population who are COVID-19 positive and are not deemed deviations from the normal course of the disease. Gastrointestinal disturbances (e.g., nausea, vomiting, diarrhea, upset stomach) are also considered symptoms of COVID-19 but will be reported as AEs as they are possible side effects of the interventions being studied.

Ethics and Dissemination

This study has received ethical approval from the research ethics boards (REB) of the Canadian College of Naturopathic Medicine (CCNM) and the Ottawa Health Sciences Network (OHSN), as well as regulatory approval from both the Therapeutic Products Directorate (TPD) and Natural and Non-Prescription Health Products Directorate (NNHPD) of Health Canada.

All amendments to the protocol will be reviewed by both REBs and submitted to the NNHPD and the TPD as either a Clinical Trial Notification or Clinical Trial Application Amendment. Both the

principal investigator and qualified investigator will sign the approved protocol prior to implementation, and each investigator and member of the research team will be adequately trained prior to carrying out any study-specific tasks after the approval of the amendment.

All participants will sign an informed consent form prior to participating in this study. Clinical staff from COVID-19 test centres will introduce the study to participants and obtain their consent to be contacted by a member of the research team. Study staff will then formally explain all aspects of the trial and answer any questions the patient may have. The patient will be given adequate time to review the consent form and no study activities will take place before the signing of the consent form.

Privacy and Confidentiality

Participant personal health information (PHI) will be kept confidential unless release is required by law. Representatives of the OHSN REB, OHRI, CCNM REB, NNHPD, or TPD may review original medical records under the supervision of Dr. Seely's staff for audit purposes.

Participants will not be identified in any publications or presentations resulting from this study, unless permission is given by the participant. All paper case report forms will be kept in locked cabinets in a locked office and all databases will be password protected on a secure server. These documents and relevant source documents will be kept for a period of 25 years as required by Health Canada. Case report forms will be shredded, and databases will be securely deleted at the end of this retention period.

Clinical Relevance

Regardless of outcome, the results of this and other similar studies will inform the public and the scientific community of the effectiveness of dietary supplements on the overall health of people

diagnosed with COVID-19 in the community and their effects on symptom severity and duration. If a positive result is seen, this study could corroborate a safe, affordable treatment option for those suffering from the virus. If a negative outcome is seen, it will help prevent patients from using unproven protection from a natural therapy and paying out of pocket for an ineffective therapy. Although there are several approved vaccines in circulation, their long-term efficacy is unknown. In addition, vaccine access is limited in low- and middle-income countries. For example, the SinoVac COVID-19 vaccine, which is currently undergoing trials in Brazil,[33] is only 51% efficacious in preventing symptomatic COVID-19.[34] Research into potential community treatments of COVID-19 continues to be important and has the potential to contribute to the worldwide public health management of this pandemic and its associated societal burden.

Dissemination and Knowledge Transfer

The work done in this study will be disseminated in the form of scientific presentations to complementary, integrative and traditional medical conferences within Canada and internationally. Presentations will be accompanied by published abstracts. The principal mechanism for knowledge transfer will be publication and will include the use of social media as well as press. We will target the most reputable clinical journal for open access publication due to the potential impact of this investigation.

Administrative Information

Protocol Revision Chronology

Protocol revision chronology can be found in the supplementary materials, section 2.0.

Trial Funding

Funding for this study was provided by the Ottawa Integrative Cancer Centre Foundation and private support from Mavis and Martin Sacher. Investigational Product for this study was provided in-kind by New Roots Herbal under the brand name Vitazan Professional.

Author Contributions

DS conceived of the study. KW, DS, ML, EC and AP conducted background review and created the study design. ML was responsible for ethical and regulatory submissions. DF provided methodological expertise and input regarding outcome selection. TR provided statistical expertise and helped formulate the statistical analysis plan. SK provided expertise in determining potential pharmacological interactions with the investigational products. All authors contributed to refinement of the protocol and approved this manuscript.

Trial Sponsor

The Ottawa Hospital Research Institute

Chief Operating Officer – Debra Lynkowski

501 Smyth Road, Ottawa ON K1H 8L6

Email: dlynkowski@ohri.ca; Phone: 613-737-8899 ext. 76815

Sponsor and Funder Statement

The funder had minimal input with regards to the investigational products used in this study. The sponsor did not have any role in the study design. Both parties will not have any role during the study with regards to its execution, analyses, interpretation of the data, or decision to submit for publication.

Patient and Public Involvement

No patients or public persons were involved.

Declaration of Interests

The authors have no competing interests to declare.

Access to Data

Datasets utilized in this study are available by request only. Please contact the trial coordinator, Mark Legacy, for access to a dataset or a copy of the current study protocol.

Trial Update

As of September 1st, 2021 we have screened five patients and currently have zero participants enrolled. Screening and recruitment continues to take place at a single centre in Ottawa, Ontario, Canada. No changes have been made to the protocol since the third revision submitted to both REBs May 4th, 2021.

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Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

Supplementary Materials

Table of Contents

Table S1: Study Validation Template

Dietary Supplements for COVID-19: Data Validation Plan	Tester	Test Date	Verifier	Verification Date
Data Entry and Correctness: Correct data types for fields. No unbounded or missing data, and no extra points where the field is limiting.				
Data Entry Tracking: Shown at the bottom of every form in the electronic database field. This includes original data entry and future corrections.				
Security: Only authorized personnel with access to the network can access this password-protected file. Limitations will also be tested.				
Software and Hardware Verification: Certified and tested on both Windows 7 and 10 to ensure compatibility				
Functional Tests				
Normal or Expected Conditions Test: Tests must be performed on all critical variables.				
Abnormal or Unexpected Conditions Test: Unexpected values, or invalid data entry error messages, must be clear and shown to the user. Skipping rules, warnings, and error messages must be documented and tested.				
Branches, Data Flow, and Combinations of Inputs Test: includes navigation through the database.				
Stress Situations: performed to account for multiple users accessing the database at the same time: no overlapping, duplication, or crashing.				
Structural Tests				
Structural tests will be performed manually by the research team. Data exports will be checked for accuracy to the eCRF. This process will be individually documented.				

2.0 Protocol Revision Chronology

Table S2: Protocol Revision Chronology

Version	Changes
1 - 2021-01-29	Original Protocol
2 - 2021-04-16	• Sponsor changed to Ottawa Hospital Research Institute (OHRI) • Allowed participants to take unused product to their local pharmacy for destruction • Added concomitant medications and stopping rules • Signatures now obtained through Adobe Sign
3 – 2021-05-04 (current protocol)	• Added eligibility criteria: participants must be tested by RT-PCR, participants must not have allergy to product ingredients • Added procedures for standard of care and hospitalization • Added official table for schedule of events • Indicated primary analysis in intention to treat • Added apparent decrease in uric acid levels as expected adverse event

Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

SPIRIT Checklist

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	Table S2
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	22
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups	16, 17

		overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Separate Document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057024.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Feb-2022
Complete List of Authors:	Legacy, Mark; Ottawa Hospital Research Institute, Clinical Epidemiology Program; The Centre for Health Innovation, Research Seely, Dugald; Canadian College of Naturopathic Medicine, Research; The Centre for Health Innovation, Research Conte, Ellen; Canadian College of Naturopathic Medicine, Research; The Centre for Health Innovation, Research Psihogios, Athanasios; Canadian College of Naturopathic Medicine, Research; The Centre for Health Innovation, Research Ramsay, Tim; Ottawa Hospital Research Institute, CEP Fergusson, Dean; Ottawa Hospital Research Institute, Clinical Epidemiology Kanji, Salmaan; The Ottawa Hospital, Department of Pharmacy; Ottawa Hospital Research Institute, Clinical Epidemiology Program Simmons, John-Graydon; Ottawa Hospital Research Institute, Clinical Epidemiology Program Wilson, Kumanan; Ottawa Hospital Research Institute, Clinical Epidemiology Program
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Epidemiology, Respiratory medicine
Keywords:	COMPLEMENTARY MEDICINE, COVID-19, Clinical trials < THERAPEUTICS

Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

Mark Legacy, BSc[1,2], Dugald Seely, ND, MSc[2,3] ND, MSc, Ellen Conte, ND[2,3], Athanasios Psihogios, ND (Inactive)[2,3], Tim Ramsay, PhD[1], Dean A. Fergusson, PhD[1], Salmaan Kanji, BSc, PharmD[1,4], John-Graydon Simmons, MD[1], Kumanan Wilson, MD[1]

1 – Ottawa Hospital Research Institute, Ottawa ON, Canada; 2 – The Centre for Health Innovation, Ottawa, ON, Canada; 3 – Canadian College of Naturopathic Medicine, Toronto, ON, Canada; 4 – The Ottawa Hospital Department of Pharmacy, Ottawa ON, Canada

Corresponding Author:
Dr. Dugald Seely, ND, MSc
Founder & CEO; The Centre for Health Innovation (CHI)
Executive Director; Patterson Institute for Integrative Oncology Research; Canadian College of Naturopathic Medicine (CCNM)
Adjunct Professor; School of Public Health and Epidemiology; Faculty of Medicine; University of Ottawa
Affiliate Investigator; Ottawa Hospital Research Institute (OHRI)
Fellow to the American Board of Naturopathic Oncology (FABNO)
429 MacLaren Street, Ottawa ON K2P 0M7
613-792-1222 ext. 2
dseely@ccnm.edu
dseely@thechi.ca

Key Terms

Complementary medicine, COVID-19, clinical trial, dietary supplements, integrative medicine, natural health products, vitamin C, vitamin D, vitamin K2, zinc

Word Count: 3988

License Statement

Abstract

Introduction

Coronavirus Disease 2019 (COVID-19) has caused morbidity, hospitalizations, and deaths worldwide. Despite four approved vaccines for COVID-19 in Canada, there is still a need for effective treatments, especially for people in the community. Vaccine efficacy is not 100% and long-term efficacy is still unknown. Furthermore, there are challenges to herd immunity including vaccine hesitancy and underlying conditions preventing vaccination. We aim to explore if the nutrients vitamin C, vitamin D, vitamin K2, and zinc are an effective treatment option for outpatients diagnosed with COVID-19. The primary outcome is the difference in participant-reported overall health; secondary outcomes include the effect on health status, symptom severity and duration, frequency and length of hospitalizations, and mortality.

Methods and Analysis

This study is a two-arm, parallel group, double-blind, placebo-controlled, phase III randomized controlled trial. 200 patients will be recruited remotely from COVID-19 test centres in Ottawa, Canada associated with The Ottawa Hospital. Overall health will be measured using the EuroQol Visual Assessment Scale; health status will be measured using the EuroQol 5-dimension 5-level

questionnaire; symptom severity and duration will be measured using an independently developed questionnaire; analyses will use an area under the curve approach and compare mean scores using unadjusted t tests. Study data will be recorded on electronic case report forms using the Research Electronic Data Capture platform. An independent data safety and monitoring board will perform ongoing review of the study for feasibility and safety.

Ethics and Dissemination

This study has received ethical approval from the research ethics boards of the Canadian College of Naturopathic Medicine and the Ottawa Health Sciences Network, as well as regulatory approval from the Therapeutic Products Directorate and Natural and Non-Prescription Health Products Directorate of Health Canada. Results will be published in a peer-reviewed scientific journal with open access.

Registration

This study is registered at https://clinicaltrials.gov: NCT04780061

Article Summary

Strengths and Limitations

- Blinding, randomization, and placebo control enhance the trial's validity.
- Large spectrum of outcomes allows for both rigorous and exploratory analyses.
- The study procedures regarding remote screening, recruitment, follow-up, and product dispensation are novel in this field and will act as a framework for future research.
- Virtual nature of the study and necessity for internet literacy may create selection bias.

- Variable length of time from symptom onset to treatment commencement due to delays in result reporting may reduce the effectiveness of the investigational product.

Introduction

Background and Rationale

Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused hospitalizations, morbidity, and deaths worldwide. COVID-19 causes mild to moderate flu-like symptoms in most people, and can cause severe disease including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death particularly in high-risk individuals.[1] As of June 2021, over 177 million people have been diagnosed with COVID-19 and over 3.8 million deaths have occurred as a result of infection.[2]

There are currently four approved COVID-19 vaccines in Canada.[3] Despite this, effective treatments are still needed. None of the four vaccines are 100% effective, and long-term immunity is yet to be determined.[4] In addition, there are challenges to achieving herd immunity based on an inability for those with certain underlying conditions to be vaccinated and vaccine hesitancy.[5] Treatments for COVID-19 are currently limited. In Canada, the only approved treatments are Remdesivir and the monoclonal antibodies Bamlanivimab, Casirivimab, and Imdevimab.[6] Remdesivir is indicated for COVID-19 positive patients with pneumonia needing supplemental oxygen; however, results from trials are mixed.[7,8] The three monoclonal antibodies are indicated for people with mild to moderate COVID-19 who are at high risk for progressing to hospitalization or death.[9,10] All three monoclonal antibody treatments are permitted under an interim authorization pending the results of clinical trials to verify their clinical benefit. To date, there are no fully approved treatments for non-hospitalized patients diagnosed with COVID-19.

The use of natural health products (NHPs), including vitamins, minerals, and herbs, to treat COVID-19 infections has received both academic and public attention.[11,12] Various NHPs have undergone observational and clinical research for a wide variety of other upper respiratory tract infections (URTIs). These trials have mainly focused on the treatment of URTI symptoms, including reducing the duration and severity of the illness. Some of the most heavily researched NHPs include andrographis,[13,14] quercetin,[15] vitamin C,[16-18] vitamin D,[19-21] and zinc.[22] At the time of the creation of this protocol (January 2021), there was observational evidence to support some NHPs for the treatment of COVID-19, such as vitamin D[23,24] and vitamin K;[25] however, there were no published double-blind, placebo-controlled, randomized clinical trials studying NHPs and COVID-19 symptoms.

A more recent review of the literature revealed the presence of new COVID-19-specific NHP research. A June 2021 meta-analysis of ten observational studies and three randomized controlled trials (RCT) (n = 2933) reported that supplementation with vitamin D significantly reduced ICU admissions and mortality, while reducing the risk of adverse outcomes, exclusively when administered after a COVID-19 diagnosis.[26] One RCT applying similar interventions as our protocol (8,000 mg ascorbic acid and 50 mg zinc gluconate) found a non-statistically significant benefit for each supplement on their own, and in combination, compared to standard care.[27] Of note, the study was terminated early due to being underpowered because of recruiting less than half of the intended sample size, and experienced considerable compliance issues.

Based on the above studies for COVID-19 and other similar URTIs, the nutrients vitamin C, vitamin D3, vitamin K2, and zinc stood out as the most promising NHPs for the treatment of symptoms caused by COVID-19, and thus were chosen as interventions for this study.

Choice of Comparator

The comparator in this trial will be a placebo. Currently, there are no standard of care treatments for people in the community diagnosed with COVID-19; thus, a placebo offers the most rigorous assessment of efficacy while having no detriment to safety due to lack of standard treatments. Should a participant be hospitalized, they will be asked to stop all study activities, including taking investigational product, until they are back home and able to tolerate the intervention again. If hospital-initiated treatments continue while at home, these will take priority over the study intervention if there is a safety concern identified by the qualified investigator or treating physician. As the investigational products in this study are readily available over the counter, monitoring for contamination and cross-over is imperative. This will be accomplished through weekly follow-up with all participants.

Objectives

We hypothesize that supplementation with vitamin D3, vitamin C, vitamin K2, and zinc will increase participant-reported overall health in outpatients diagnosed with COVID-19 compared to a placebo by reducing the severity and duration of common COVID-19 symptoms experienced in a community setting.

The primary objective of this study is the difference in participant-reported overall health between arms; secondary objectives include:

1. Effect of the intervention on the health status of participants
2. Symptom severity including self-reported measures for fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, shakes/chills, congestion, and loss of taste and smell

3. Total symptom duration
4. Incidence of delayed return to usual health
5. Frequency of hospitalizations, including emergency room (ER) visits, acute care admissions, and intensive care unit (ICU) admissions
6. Hospital length of stay (if applicable)
7. All-cause mortality

Study Design

This study is a two-arm, parallel group, double-blind, placebo-controlled, phase III trial powered to detect meaningful differences in the overall health of adults with COVID-19 between the treatment and control arms at 21 days. Total trial duration for participants is 12 weeks, and the treatment period runs for 21 days following randomization.

Participants, Interventions, and Outcomes

Study Setting

This study will recruit outpatients from Ottawa, Canada from COVID-19 test centres in the community associated with The Ottawa Hospital (TOH). The primary site of study conduct will be the Centre for Health Innovation (CHI), an integrative care clinic located in Ottawa. All recruitment, study activities, and follow-up will take place remotely as participants will be in quarantine for at least 14 days. Study staff will only communicate with participants by phone or email, and participants will complete all study activities in their own homes.

Eligibility Criteria

To be eligible for this study, patients must meet the following inclusion criteria:

1. Adults (≥18) who test positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) in an outpatient setting
2. Access to internet

The criterion of access to internet may cause selection bias in our population and will not be entirely representative of COVID-19-positive patients in the Ottawa community; however, due to the nature of the study, the progression of the disease, and the public health recommendations to maintain both safety of participants and research staff, in-person consent and follow-up is not feasible.

In addition, patients must not exhibit any of the following exclusion criteria:

1. Symptom onset greater than 4 days prior to enrolment
2. Regular supplementation with >500 mg vitamin C, >1000 units vitamin D (any form), >120 mcg vitamin K (any form), or >15 mg zinc taken daily within the past month
3. Currently taking warfarin or an equivalent vitamin K antagonist anticoagulant
4. End stage chronic kidney disease
5. History of calcium oxalate kidney stones
6. Active granulomatosis (sarcoidosis, tuberculosis, lymphoma)
7. Known hypercalcemia or hypervitaminosis D
8. Currently taking either of the following antibiotics: cephalexin, tetracyclines
9. Known allergy to any investigational product, silicon dioxide, cellulose, or medium chain triglyceride oil
10. Participating in an investigational study or participation in an investigational study within the past 30 days

The first exclusion criterion was chosen in an attempt to include patients who have the best chance at a potential benefit from the intervention. The median time to symptom resolution for COVID-19 patients has been reported to be 4-8 days;[28] therefore, recruitment of patients whose symptom onset date was 5 or more days before enrolment would likely yield a large proportion of patients whose symptoms have already resolved. The second exclusion criterion balances feasibility with contamination. Those supplementing with one or more of the investigational products could introduce bias to the population and skew results; however, low-dose supplementation is common amongst Canadians and would severely hinder recruitment.

Interventions

The interventions for this study will be vitamin C, vitamin D3, vitamin K2, and zinc plus equivalent placebos. All investigational products will be manufactured by New Roots Herbal under the brand name Vitazan Professional. Specific formulations of each investigational product are as follows:

Study Product #1: Vitamin D3 50,000 IU

Formulation: Capsule. Each capsule contains 500 mg (50,000 units) cholecalciferol (vitamin D3)

Dose: One capsule on day 1 of the intervention period

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis

Study Product #2: Vitamin K2/D3 Liquid

Formulation: Liquid. Each 0.0285 mL drop contains 30 mcg menaquinone-7 (MK-7, vitamin K2) and 3.125 mcg (125 units) cholecalciferol.

Dose: 0.114 mL (four drops) twice daily for 21 days totalling 240 mcg MK-7 and 1,000 units cholecalciferol per day.

Placebo Equivalent: Medium chain triglyceride oil

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis; warfarin or another vitamin K antagonist anticoagulant

Study Product #3: Vitamin C/Zinc acetate

Formulation: Capsule. Each capsule contains 666 mg ascorbic acid (vitamin C) and 8.3 mg zinc acetate

Dose: Three capsules three times daily for 21 days totalling 6 g ascorbic acid and 75 mg zinc acetate per day.

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: calcium oxalate kidney stones, end stage chronic kidney disease, cephalexin, tetracycline antibiotics

Modifications to the intervention schedule are permitted under the discretion of the qualified investigator (KW) or sub-investigator delegated the task. Adherence to the protocol will be participant-reported through a phone call at the end of the intervention period. Participants will be asked to conduct pill counts for the two capsule-based products and estimate how many doses they have missed of the liquid product.

Absolute contraindications to the investigational products are outlined above and in the exclusion criteria. Should a participant be placed on one of these medications or be diagnosed with one of

the conditions, they will stop taking the study product. There are no rescue medications for this study.

Outcomes, Timeline, and Schedule of Events

The full schedule of events is presented in table 1. The primary outcome of this study is the difference in mean participant-reported overall health over 21 days between arms measured using the EuroQol Visual Assessment Scale (EQ-VAS).[29] The EQ-VAS records the respondent's overall current health on a vertical scale between 0 and 100, where the end points are labelled "the best health you can imagine" (i.e., a score of 100) and "the worst health you can imagine" (i.e., a score of 0). The EQ-VAS will be filled out each day while on the intervention (21 days total). The secondary outcomes are as follows:

Health Status: Measured by combining one level from each of the five dimensions of the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire[29] to form a unique health state. The EQ-5D-5L questionnaire will be filled in at baseline and weeks 1, 2, 3, 4, 8, and 12. Mean health state at each time point will be compared between arms.

Symptom Severity & Duration: Measured using an internally-developed questionnaire specific for the most common COVID-19 symptoms, which include: fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, chills, altered taste, altered smell, and nasal congestion.[28,30] Each symptom will be rated on a 4-point severity scale: 0-none, 1-slight, 2-moderate, and 3-severe. Participants will fill in this questionnaire daily while receiving treatment (i.e., for 21 days). We will compare the total mean symptom scores over 21 days between arms.

Incidence of delayed return to usual health: Measured through follow-up calls with participants at weeks 4, 8, and 12 following randomization. Those experiencing prolonged COVID-19 symptoms lasting 4-12 weeks will be classified as having "ongoing symptomatic COVID-19," while those still afflicted at 12 weeks will be classified as having "post-COVID-19-syndrome."[31] We will compare the number of participants in each arm who exhibit ongoing symptomatic COVID-19 and post-COVID-19 syndrome.

Hospitalization: the rate and type of hospitalization, as well as the length of stay, will be collected from participant medical records where possible and will otherwise be participant-reported. Information will be collected throughout the 12-week study period.

All-Cause Mortality: date of death will be collected through medical records and obituary searches when medical records are not available. Information will be collected throughout the 12-week study period.

Overall health was chosen as the primary outcome as it uses a validated tool and is easily interpretable. Although research on other URTIs focuses heavily on symptom severity questionnaires, currently there are no validated tools for assessing COVID-19 symptom severity. The clinical significance of symptom severity in a non-validated tool is much more difficult to analyze and open to differing interpretations.

The symptom questionnaire developed by our team is largely based on recommendations from the US Food and Drug Administration guidance document for investigators conducting community clinical trials for COVID-19 prevention or treatment[32] and commonly reported COVID-19 symptoms in both the hospital and community setting.[28,30]

Sample Size

With respect to the primary outcome of participant-reported overall health, power calculations were conducted based on between-group differences and Cohen's guideline for a small effect size of 0.3. A sample size of 176 (88 per arm) provides 80% power to detect a difference at an alpha of 0.05. To account for an approximate 10-15% loss to follow-up we will enrol 200 participants (100 per arm).

Recruitment

Screening for potential participants will be facilitated by clinical staff at COVID-19 test centres in Ottawa associated with TOH. Staff at these test centres are responsible for contacting any person who tests positive for COVID-19. The clinical team will use this opportunity to obtain the patient's consent to be contacted by the research team. Nursing staff will notify the trial coordinator of all patients who agree to be contacted. Study staff at the CHI will then contact each patient by phone and further determine their eligibility. If a patient is interested and eligible, they will be taken through the informed consent process and sign an electronic informed consent form using Adobe Sign.

Over time, the COVID-19 case count in Ottawa has varied greatly. With vaccine distribution continuing to increase, we assume the infection rate will remain steady at 10-15 diagnoses per day; however, not all COVID-19 positive patients will be referred to our group due to competing trials and lack of recruitment from all test centres. We expect to receive referrals for 50% of all people diagnosed with COVID-19. Based on previous trials we have conducted with natural health products and input from the investigators, we assume 50% of people will be eligible for this study,

and 50% of those eligible will be interested in participating. This yields an approximate expected recruitment rate of 1-2 participants per day, and an expected recruitment period of 3-6 months.

Table 1: Schedule of Events

	Time of Assessment										
	Screening (pre-enrolment)	Baseline (Prior to intervention)	Days 1-6	Day 7	Days 8-13	Day 14	Days 15-20	Day 21	Week 4	Week 8	Week 12
Eligibility	✓										
Informed Consent	✓										
Randomization		✓									
Medical History & Current Medications		✓									
Demographics		✓									
Study Intervention			✓	✓	✓	✓	✓	✓			
EQ-VAS			✓	✓	✓	✓	✓	✓			
Symptom Questionnaire			✓	✓	✓	✓	✓	✓			
EQ-5D-5L		✓		✓		✓		✓	✓	✓	✓
Phone Call Follow-Up • Concomitant Medications • Adverse Events • Hospitalizations • Delayed return to usual health				✓		✓		✓	✓	✓	✓

EQ-VAS: EuroQol Visual Assessment Scale; EQ-5D-5L: EuroQol 5-Dimension 5-Level. EQ-VAS and symptom questionnaires must be filled in on the appropriate days. A 3-day window will be allowed for EQ-5D-5L completion and phone call follow-up for the first 4 weeks. The window will increase to 5 days for weeks 8 and 12. Compliance to the intervention will be participant-reported and take place on day 21 or week 4.

Study Methods

Assignment of Interventions

Eligible participants will be randomized using a web-based system developed and maintained by the Ottawa Methods Centre (OMC), an organization that provides consultation services for areas such as research methodology, biostatistics, and data management. Randomization will occur in permuted blocks of 4 and 6 at ratio of 1:1 to one of the following groups: (1) nutrient therapy with vitamin D, vitamin C, vitamin K2, and zinc or (2) placebo. All study staff, treating physicians and participants will be blinded to the allocation. The staff at Vitazan Professional will be the only personnel with knowledge of treatment allocation to facilitate shipment of study product directly to participants. Patients will be randomized once they sign an informed consent form and have their eligibility confirmed by a medical doctor. If un-blinding is deemed to be necessary, the trial coordinator will request the treatment allocation from the OMC or Vitazan Professional.

Data Collection and Management

Study data will be collected on paper case report forms (CRF) or electronic case report forms (eCRF) using the Research Electronic Data Capture (REDCap) platform. All study data, including paper CRFs, eCRFs, and the electronic database, will be managed by the trial coordinator (ML) under the supervision of the principal investigator (DS). Participants will be able to use the REDCap platform to directly enter data or may choose to fill in paper CRFs. To facilitate direct entry to an eCRF, participants will receive an email with a direct link to the eCRF where they can enter their responses. Study data in REDCap will be stored on a secure server located in Toronto, Canada managed by the Canadian College of Naturopathic Medicine. Paper CRFs will be kept at the CHI in locked cabinets.

REDCap has been tested to work on Windows 10, the standard software package at the CHI, as well as Mac OS Catalina and above. As required by Health Canada, the REDCap database has been validated by the study team and is designed to keep track of all users who enter, save, edit, and update data entered to the eCRFs, and to automatically provide a timestamp of all activity. See *Supplementary Materials* section 1.0 for an outline of the data validation plan.

Statistical Methods

All analyses will follow an intention to treat approach. Continuous and quasi-continuous variables (participant-reported health & health status, symptom severity, and length of stay) will be compared between arms using unadjusted t-tests. Dichotomous outcomes (delayed return to usual health, hospitalizations and deaths) will be compared between arms using Chi-square tests or Fisher's exact tests where appropriate. Time to symptom resolution will be displayed graphically with Kaplan-Meier curves and differences between arms will be compared with a log-rank test.

Safety and Data Monitoring

External oversight for this trial will be provided by an independent data safety and monitoring board (DSMB). The DSMB will meet either in-person or remotely to discuss matters related to the safety of study participants, validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol and data completeness. The DSMB will review interim data once 100 participants are enrolled or after 4 months, whichever comes first. The DSMB may choose to review data at other times at their discretion. Based on review of the safety data, the DSMB may recommend continuation of the study without modification(s), study interruption, study termination, or modification(s) of the trial.

Additionally, the trial will have a quality control monitoring process in place to verify that all data are accurate and complete. Investigators will permit trial-related monitoring, audits and regulatory inspections, and direct access to source data/documents. The monitor will generate a site monitoring report for the qualified investigator detailing significant findings, deviations, deficiencies, plausibility, record completeness and any corrective actions required.

Adverse events (AE) will be collected by the study team for each participant throughout the intervention period plus one additional week using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Classic or other symptoms of COVID-19 will not be recorded as AEs. These include fever, new or worsening cough, shortness of breath/difficulty breathing, fatigue, myalgia/arthralgia, sore throat, sputum production, dysphagia, new olfactory or taste disorders, pneumonia, rhinorrhea, chills/shakes, or nasal congestion. Such events are expected in a population who are COVID-19 positive and are not deemed deviations from the normal course of the disease. Gastrointestinal disturbances (e.g., nausea, vomiting, diarrhea, upset stomach) are also considered symptoms of COVID-19 but will be reported as AEs as they are possible side effects of the interventions being studied.

Patient and Public Involvement

No patients or public persons were involved.

Ethics and Dissemination

This study has received ethical approval from the research ethics boards (REB) of the Canadian College of Naturopathic Medicine (CCNM) and the Ottawa Health Sciences Network (OHSN), as well as regulatory approval from both the Therapeutic Products Directorate (TPD) and Natural and Non-Prescription Health Products Directorate (NNHPD) of Health Canada.

All amendments to the protocol will be reviewed by both REBs and submitted to the NNHPD and the TPD as either a Clinical Trial Notification or Clinical Trial Application Amendment. Both the principal investigator and qualified investigator will sign the approved protocol prior to implementation, and each investigator and member of the research team will be adequately trained prior to carrying out any study-specific tasks after the approval of the amendment.

All participants will sign an informed consent form prior to participating in this study. Clinical staff from COVID-19 test centres will introduce the study to participants and obtain their consent to be contacted by a member of the research team. Study staff will then formally explain all aspects of the trial and answer any questions the patient may have. The patient will be given adequate time to review the consent form and no study activities will take place before the signing of the consent form.

Privacy and Confidentiality

Participant personal health information (PHI) will be kept confidential unless release is required by law. Representatives of the OHSN REB, OHRI, CCNM REB, NNHPD, or TPD may review original medical records under the supervision of Dr. Seely's staff for audit purposes.

Participants will not be identified in any publications or presentations resulting from this study, unless permission is given by the participant. All paper case report forms will be kept in locked cabinets in a locked office and all databases will be password protected on a secure server. These documents and relevant source documents will be kept for a period of 25 years as required by Health Canada. Case report forms will be shredded, and databases will be securely deleted at the end of this retention period.

Clinical Relevance

Regardless of outcome, the results of this and other similar studies will inform the public and the scientific community of the effectiveness of dietary supplements on the overall health of people diagnosed with COVID-19 in the community and their effects on symptom severity and duration. If a positive result is seen, this study could corroborate a safe, affordable treatment option for those suffering from the virus. If a negative outcome is seen, it will help prevent patients from using unproven protection from a natural therapy and paying out of pocket for an ineffective therapy. Although there are several approved vaccines in circulation, their long-term efficacy is unknown. In addition, vaccine access is limited in low- and middle-income countries. For example, the SinoVac COVID-19 vaccine, which is currently undergoing trials in Brazil,[33] is only 51% efficacious in preventing symptomatic COVID-19.[34] Research into potential community treatments of COVID-19 continues to be important and has the potential to contribute to the worldwide public health management of this pandemic and its associated societal burden.

Dissemination and Knowledge Transfer

The work done in this study will be disseminated in the form of scientific presentations to complementary, integrative and traditional medical conferences within Canada and internationally. Presentations will be accompanied by published abstracts. The principal mechanism for knowledge transfer will be publication and will include the use of social media as well as press. We will target the most reputable clinical journal for open access publication due to the potential impact of this investigation.

Administrative Information

Protocol Revision Chronology

Protocol revision chronology can be found in the supplementary materials, section 2.0.

Trial Funding

Funding for this study was provided by the Ottawa Integrative Cancer Centre Foundation and private support from Mavis and Martin Sacher. Investigational Product for this study was provided in-kind by New Roots Herbal under the brand name Vitazan Professional.

Author Contributions

DS conceived of the study. KW, DS, ML, EC and AP conducted background review and created the study design. ML was responsible for ethical and regulatory submissions. DF provided methodological expertise and input regarding outcome selection. TR provided statistical expertise and helped formulate the statistical analysis plan. SK provided expertise in determining potential pharmacological interactions with the investigational products. All authors contributed to refinement of the protocol and approved this manuscript.

Trial Sponsor

The Ottawa Hospital Research Institute

Chief Operating Officer – Debra Lynkowski

501 Smyth Road, Ottawa ON K1H 8L6

Email: dlynkowski@ohri.ca; Phone: 613-737-8899 ext. 76815

Sponsor and Funder Statement

The funder had minimal input with regards to the investigational products used in this study. The sponsor did not have any role in the study design. Both parties will not have any role during the study with regards to its execution, analyses, interpretation of the data, or decision to submit for publication.

Declaration of Interests

The authors have no competing interests to declare.

Access to Data

Datasets utilized in this study are available by request only. Please contact the trial coordinator, Mark Legacy, for access to a dataset or a copy of the current study protocol.

Trial Update

As of September 1st, 2021 we have screened five patients and currently have zero participants enrolled. Screening and recruitment continues to take place at a single centre in Ottawa, Ontario, Canada. No changes have been made to the protocol since the third revision submitted to both REBs May 4th, 2021.

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Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

Supplementary Materials

Table of Contents

Table S1: Study Validation Template

Dietary Supplements for COVID-19: Data Validation Plan	Tester	Test Date	Verifier	Verification Date
Data Entry and Correctness: Correct data types for fields. No unbounded or missing data, and no extra points where the field is limiting.				
Data Entry Tracking: Shown at the bottom of every form in the electronic database field. This includes original data entry and future corrections.				
Security: Only authorized personnel with access to the network can access this password-protected file. Limitations will also be tested.				
Software and Hardware Verification: Certified and tested on both Windows 7 and 10 to ensure compatibility				
Functional Tests				
Normal or Expected Conditions Test: Tests must be performed on all critical variables.				
Abnormal or Unexpected Conditions Test: Unexpected values, or invalid data entry error messages, must be clear and shown to the user. Skipping rules, warnings, and error messages must be documented and tested.				
Branches, Data Flow, and Combinations of Inputs Test: includes navigation through the database.				
Stress Situations: performed to account for multiple users accessing the database at the same time: no overlapping, duplication, or crashing.				
Structural Tests				
Structural tests will be performed manually by the research team. Data exports will be checked for accuracy to the eCRF. This process will be individually documented.				

2.0 Protocol Revision Chronology

Table S2: Protocol Revision Chronology

Version	Changes
1 - 2021-01-29	Original Protocol
2 - 2021-04-16	• Sponsor changed to Ottawa Hospital Research Institute (OHRI) • Allowed participants to take unused product to their local pharmacy for destruction • Added concomitant medications and stopping rules • Signatures now obtained through Adobe Sign
3 – 2021-05-04 (current protocol)	• Added eligibility criteria: participants must be tested by RT-PCR, participants must not have allergy to product ingredients • Added procedures for standard of care and hospitalization • Added official table for schedule of events • Indicated primary analysis in intention to treat • Added apparent decrease in uric acid levels as expected adverse event

Dietary Supplements to Reduce Symptom Severity and Duration in People with SARS-CoV-2: Study Protocol for a Randomized, Double Blind, Placebo Controlled Clinical Trial

SPIRIT Checklist

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	Table S2
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	22
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups	16, 17

		overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Separate Document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A