Clinical trial of Ashwagandha for promoting recovery from COVID-19 in the UK

Short title: Ayurveda for Promoting Recovery In Long COVID (APRIL Trial)

TRIAL PROTOCOL V4.1

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SPONSOR: London School of Hygiene & Tropical Medicine (LSHTM, UK)

FUNDER: Ministry of AYUSH, Government of India (through the All India Institute of Ayurveda (AIIA), an autonomous institution under the Ministry of AYUSH)

STUDY COORDINATION CENTRE: LSHTM (UK)

Study Summary

Title: Clinical trial of Ashwagandha for promoting recovery from Covid-19 (APRIL)

Design: Randomised double-blind placebo-controlled trial

Aims: To examine whether Ashwagandha tablets are effective for promoting recovery from long-term symptoms of Covid-19 in the UK

Treatment: Ashwagandha root extract (1000mg daily dose, taken as 2x250mg twice daily (morning and evening) for 3 months) or matching placebo

Primary outcome:

Self-reported functional status (Post COVID-19 Functional Status Scale) at 3 months.

Secondary outcomes:

i) Quality of life by PROMIS 29+2 summary score, ii) Self-reported fatigue, pain, sleep, anxiety, depression and social, physical and cognitive function by PROMIS 29+2 individual dimensions, iii) Self-reported breathlessness by modified MRC Dyspnoea Scale, iv) Health utility by EQ 5D-5L utility score, v) Work status and productivity, vi) Other self-reported symptoms, vii) total adverse events (all at 3 months).

Population: UK adults, N=2500 (1250 intervention, 1250 placebo).

Eligibility: Adults (18 years or older) who have a current diagnosis of Long COVID, defined as per NICE guideline on Long COVID (NG188), , meet the other clinical screening criteria (i.e. without severe psychiatric disorder, liver test abnormalities, active malignancy, not pregnant, etc), and who are willing and able to complete the study protocols (take trial medication daily for 3 months and complete monthly clinical monitoring and online or postal questionnaires).

Duration: Ten months (recruitment phase 7 months, follow-up 3 months)

Key Words:

Ayurveda, Ashwagandha, Covid-19, Long COVID, post-COVID syndrome, randomized controlled trial, double blinded, functional status, quality of life, symptoms.

Signature page

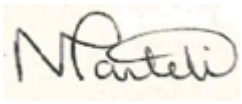
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the International Council for Harmonisation Good Clinical Practice (ICH GCP) and/or Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the Sponsor's (and any other relevant) Policies and Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Name: **Naomi Panteli** **Role:** Research Governance and Integrity Officer

Signature:  **Date: 01/04/2025**

Chief Investigator:

Name: **Sanjay Kinra**

Signature 

Date: 25/03/2025

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Please contact the Trial Manager for general queries, supply of trial documentation, and collection of data.

Clinical Queries

Clinical queries should be directed to the relevant investigator, or to the trial manager who will direct the query to the appropriate person.

Sponsor

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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Funder

This study is funded by the Ministry of AYUSH, Government of India (through the All India Institute of Ayurveda (AIIA), an autonomous institution under the Ministry of AYUSH)

About this protocol

This protocol describes the 'Clinical trial of Ashwagandha for promoting recovery from COVID-19 in the UK' study and provides information about procedures for entering participants as well as the design and reporting features. Every care has been taken in its drafting, but corrections or amendments may be necessary.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

Note on the spelling of Ashwagandha

Ashwagandha can be spelt in multiple different ways. The most common spelling seen in English is "Ashwagandha", which we have therefore chosen as the spelling for the trial title, all public facing documents/communication, and throughout this document. The preferred spelling in the Ayurvedic Pharmacopoeia of India is "Asvagandha", which is the spelling used in the Investigational Medicinal Product Dossier (IMPD) and associated Qualified Person (QP) declaration. We intend or imply no difference in meaning by use of these alternative spellings; they should be read interchangeably.

Other common spellings of Ashwagandha include Asavagandha, Ashvagandha and Asgandh. Ashwagandha is an extract of the roots of the plant Withania somnifera, and in some literature the extract is also referred to as "Withania somnifera". Other common names for the plant include winter cherry and Indian ginseng.

Abbreviations

AE – Adverse Event

AIIA - All India Institute of Ayurveda

AR – Adverse Reaction

CI - Chief Investigator

Co I - Co Investigator

COVID-19 - Coronavirus disease 2019

CTCAE – Common Terminology Criteria for Adverse events

DMC - Data Monitoring Committee

GDPR – General Data Protection Regulation

GMP – Good Manufacturing Practice

GP – General Practitioner

IB- Investigator's Brochure

ICH GCP - International Conference on Harmonisation Good Clinical Practice

IMP – Investigational Medicinal Product

IMPD – Investigational medicinal product dossier

LSHTM - London School of Hygiene & Tropical Medicine

MHRA- Medicines and Healthcare products Regulatory Agency

QP – Qualified Person

REC - Research Ethics Committee

HRA - Health Research Authority

SAE - Serious Adverse Event

SAR- Serious Adverse Reaction

SARS-CoV-2- Severe Acute Respiratory Syndrome Coronavirus 2

SmPC - Summary of Product Characteristics

SOP – Standard Operating Procedure

SUSAR – Suspected Unexpected Serious Adverse Reaction

TMG - Trial Management Group

TSC - Trial Steering Committee

VO2 max - maximum Volume of Oxygen (O_2)

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1. Introduction

1.1. Background

Despite successful vaccine development, COVID-19 continues to pose a substantial threat to health in the UK and globally. More than 15% of adults in the UK (and more than 10% globally) have been infected with the SARS-CoV-2 virus[1,2]; a figure which will continue to rise due to poor vaccine uptake among certain groups and sub-optimal vaccine efficacy (potentially exacerbated by novel virus strains). Beyond the acute morbidity and mortality caused by COVID-19, there is growing concern around the disease's long-term sequelae. Often referred to as "long COVID", symptoms can include respiratory problems (chronic cough, shortness of breath, chest tightness), cognitive dysfunction, poor mental health, extreme fatigue and muscle weakness[3]. Symptoms last for 1-3 months ("ongoing symptomatic COVID-19"), or longer in many cases ("post-COVID-19 syndrome"), and are estimated to affect around 20% of COVID-19 survivors[4]. Long COVID is understood to be a multi-system disease, similar to some other post-viral syndromes, although its pathophysiology is scarcely understood, and there is little evidence around its effective treatment or management[5].

'*Ashwagandha'* (*Withania somnifera*), a traditional herb in the Indian Ayurvedic system of medicine, has been used for centuries for promoting energy and vitality, reducing stress and boosting the immune system[6]. Recently, a number of randomised placebo-controlled trials in humans have demonstrated its efficacy for reducing anxiety and stress[7,8], improving muscle strength[9,10], enhancing VO2 max[11], and reducing symptoms of fatigue in patients treated for chronic conditions[12,13]. It has also been indicated for treating non-restorative sleep, a hallmark of chronic fatigue, with trials currently ongoing[14]. This evidence, combined with emerging literature on its pharmacological and immunomodulatory effects *in vitro* and in animals[15], suggest Ashwagandha as a potential therapeutic candidate for alleviating the long-term symptoms of COVID-19. The choice of Ashwagandha also becomes easier as it is widely available as an over-the-counter nutritional supplement in the UK, and has a proven safety profile[6].

1.2. Aim

The aim of this study is to determine whether Ashwagandha can improve functional status, quality of life and alleviate symptoms in UK adults suffering from long-term symptoms of COVID-19.

1.3. Objectives

Primary – to determine the effectiveness of Ashwagandha tablets (3-month course) for improving functional status (measured by the Post-COVID-19 Functional Status Scale) among people experiencing ongoing symptoms of COVID-19.

Secondary – to determine the effectiveness of Ashwagandha tablets (3-month course) for improving quality of life, reported fatigue, breathlessness, pain, sleep quality, mental health, cognitive function, work status and other symptoms.

1.4. Trial design

This is a randomised double-blind placebo-controlled trial. Interested individuals who have a diagnosis of Long COVID (and conform to all other eligibility criteria) will be randomised to take Ashwagandha or placebo for 3 months (delivered at home by post). Follow-up for functional status, quality of life and other self-reported outcomes will be by online or postal surveys (as per participant preference) conducted monthly. Follow-up for safety will be through clinical assessment by the study investigator's clinical team, conducted monthly.

1.5. Summary of risks and benefits

Potential benefits to participants include reduced ongoing symptoms of COVID-19 as well as additional therapeutic benefits of Ashwagandha[16]. Potential risks include allergic reactions to the trial medication and side effects of the medication.

2. Methods: Participants

2.1. Study setting

Participants will be recruited through participating GP practices or NHS Long Covid Clinics (hereafter referred to as clinical trial sites). Participants will receive the trial medication to their house via post and follow-up surveys will either be conducted online, over telephone, or by postal questionnaire. Clinical monitoring will be conducted remotely or in-person at participating clinical trial sites. The trial coordinating centre is LSHTM in central London.

2.2. Eligibility criteria

Eligibility will be assessed by a study investigator based at a clinical trial site (- who may or may not be the participant's own GP) through a clinical screening assessment with participants.

Inclusion criteria:

- Adults (18 years or older) with the capacity to provide informed consent, and
- Have been diagnosed with Long COVID as per the NICE Guidelines (NG188) – that is, either one of “Ongoing symptomatic COVID-19; signs and symptoms of COVID-19 from 4 weeks up to 12 weeks”, or “Post-COVID-19 syndrome; Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed”. The diagnosis will be confirmed by the participant’s GP and/or medical records.
- Report that their Long COVID has reduced their ability to carry out day-to-day activities compared with the time before they had COVID-19.
- Willing and able to complete the study protocols (take trial medication regularly for 3 months, complete online telephone or postal surveys monthly, and participate in clinical monitoring assessment monthly)
- Not taking any other herbal medicines, or willing to stop taking any such medicines for the duration of the trial. Herbal medicine is defined as a plant or plant part, or mixture or extract of these, which is taken in medicinal form to improve health, prevent disease, or treat illness.

Exclusion criteria:

- Self-diagnosed Long COVID in the absence of a clinical diagnosis as per the NICE Guidelines
- Any medical condition or suspected medical condition which, in the opinion of the Investigator may present an unreasonable risk to the study participant as a result of his/her participation in this clinical study (this may involve conduct of any clinical assessment deemed necessary by the study investigator to confirm that this criteria is met, such as (but not limited to) validated psychiatric scales, ECGs, and laboratory tests for clinical chemistry, haematology, urinalysis, kidney function, etc).
- Previous clinical diagnosis of severe psychiatric disorders
- Abnormal liver function test results, as indicated by alanine aminotransferase or aspartate aminotransferase or total bilirubin >2 x ULN, either measured as part of routine care within past 3 months or conducted for the purposes of the clinical trial (if a recent test result is not available)
- Previous clinical diagnosis of chronic kidney disease or other medical condition associated with impaired kidney function
- Previous clinical diagnosis of heart disease or other cardiac problems

- Use of any investigational products within 5 elimination half-lives after the last dose or at screening
- History of malignancy unless resolved by adequate treatment with no evidence of recurrence
- Hypersensitivity to the active substance or to any of the excipients
- Women breastfeeding or with a positive urine pregnancy test at screening
- Women planning to become pregnant for the duration of the participation in the study
- Men and women of childbearing potential unwilling to adhere to the relevant contraception requirements for the duration of the study (until at least 24 hours after the final dose of trial medication is taken). Women of childbearing potential (WOCBP) are defined as all women who are: “fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.” Acceptable contraception methods for WOCBP in this trial include: combined hormonal contraception, progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence, or condom use. Sexual abstinence is defined as: “refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject”. Male participants are required to use condoms. All participants are required to inform investigator immediately if these contraception requirements are not met or if pregnancy is suspected.
- Participants taking benzodiazepines, anticonvulsants, barbiturates or any other CNS depressants

2.3. Recruitment

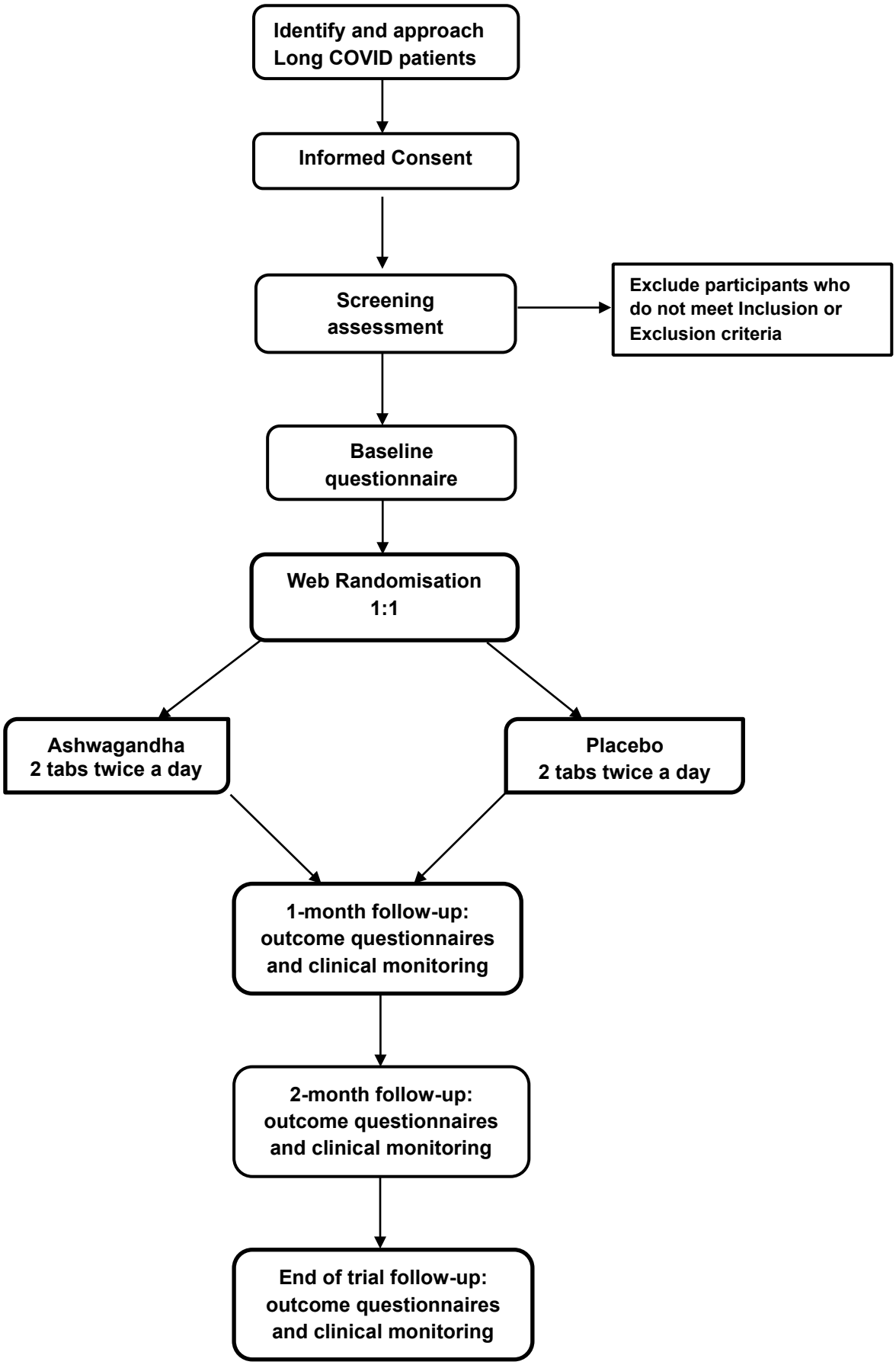
The study will be conducted in the UK. Interested and potentially eligible participants will be identified by clinical trial sites, or if appropriate, by participant identification centres local to the clinical trial sites. Potential participants will be provided study materials (information sheet, FAQs) to read, and then referred to a study investigator (who may or may not be their own GP) for recruitment into the trial. The study investigator’s team will contact referred participants to answer any questions they may have (after giving due time to read the trial information), and the investigator will obtain written informed consent (which may be

inperson, by post, or by e-consent depending on participant preference). Once consented, the investigator will conduct a screening assessment with the participant which will involve at minimum a clinical interview, review of patient medical history and review of all eligibility criteria including results of recent liver function tests. Those participants who have not had a liver function test within the past three months will have to take a liver function test at screening (with their consent obtained in the ICF). Women of childbearing potential will be asked to take a urine pregnancy test to confirm they are not pregnant. The clinical screening assessment may be conducted remotely or in person in the first instance, with further followup assessments arranged in person if deemed clinically indicated by the investigator.

All participants whose liver function test results are abnormal will not be eligible to take part in the trial and their registered GP (if different from the recruiting study investigator) will be informed by sending a letter (for which consent will be sought in the consent form) regarding their abnormal liver function test and ineligibility to take part in the trial.

Consented and eligible participants will be formally entered into the trial by the investigator, who will inform trial team at LSHTM. Participants will then be asked to complete baseline questionnaire surveys, after which they will be randomised and trial welcome packs (including information sheets and the first month of trial medication) will be dispatched to their home address by courier from LSHTM. Letters will also be prepared and sent to participant's GPs (if different from study investigator) to inform them of the participants entry into the trial (for which consent will be sought in the consent form.).

A flow chart of the recruitment and follow-up process is given in Figure 1.
Figure 1. Recruitment pathway


Identify and approach Long COVID patients
Informed Consent
Screening assessment
Exclude participants who do not meet Inclusion or Exclusion criteria
Baseline questionnaire
Web Randomisation 1:1
Ashwagandha 2 tabs twice a day
Placebo 2 tabs twice a day
1-month follow-up: outcome questionnaires and clinical monitoring
2-month follow-up: outcome questionnaires and clinical monitoring
End of trial follow-up: outcome questionnaires and clinical monitoring

2.4. Withdrawal information

Participants can choose to withdraw from the study at any time, but under UK clinical trial regulations, data of participants who withdraw will still be retained in the study database. This will be made clear in the Participant Information Sheet.

Complete withdrawal from this trial means that the participant does not wish to continue taking trial medication and does not wish to complete outcome questionnaires.

Participant who are unblinded or become pregnant will be completely withdrawn from the trial.

Partial withdrawal means that the participant does not wish to take trial medication any longer but is still willing to complete follow up outcome questionnaires.

Participants can inform their Research Doctor or Research Nurse if they do not want to take study medication or monthly investigations. They will also be provided the Trial Manager's contact details if they wish to inform the Trial Manager about their withdrawal from the study. Reason for withdrawal will be documented in the withdrawal form.

If participants withdraw but do not inform the study team, a follow-up phone call will be made to them up to 3 times to ascertain participation status in the trial. If we are unable to contact a participant at all, to check on their welfare we may reach out to their nominated contact.

Following an adverse reaction, the investigator will have rights to withdraw a participant from the trial considering participant safety. The PI or CI will have rights to withdraw a participant following significant trial medication non-compliance and protocol deviation which will be discussed with the TSC.

2.5. Deviation of protocol

Any deviations from protocol will be immediately documented by the relevant team member (investigator or trial team) and reported to the CI. The Trial Steering Committee (TSC) will be responsible for reviewing deviations from protocol. If multiple episodes of the same protocol deviation occur, then the TSC will initiate an audit and take appropriate action Any serious breaches of GCP or of the protocol must be reported to MHRA by the sponsor within 7 days of becoming aware of the breach

2.6. Schedule of trial activities

Study period	**Screening**	**Treatment cycle**												**End of trial**
Treatment cycle	Screening	cycle 1				cycle 2				cycle 3				Post-trial treatment
Cycle days	-1 to -30	1-30				31 -60				61-90				91 days plus
Study week		1	2	3	4/5	5	6	7	8/9	9	10	11	12	13
Informed Consent (e-consent or paper)	x													
Screening assessment eligibility check	x													
Liver function Test (LFT) ♦	x				x									x
Urine pregnancy test for WOCBP	x				x				x					x
Complete outcome questionnaires•	x					x				x				x
Randomisation••	x													
Posting medication and a diary ↖	x				x				x					
Trial medication 2 tabs twice a day ✶		x	x	x	x	x	x	x	x	x	x	x	x	
Clinical assessment for safety monitoring					x				x					x
Participant discharged from trial														x

♦ Liver function Test (LFT) – If the blood test has been already conducted as part of standard of care within the past 3 months then it can be used and there is no need to repeat further test unless clinically indicated. Follow-up blood tests to be done within 7 days of target date.

 Urine pregnancy test for women of child-bearing potential (WOCBP) - Urine pregnancy test will be done at screening, after completing 1st and 2nd month trial treatment and at the end of the treatment to confirm nil pregnancy. **If a female subject becomes pregnant during the Treatment period, she should immediately notify the Investigator and trial medication should be permanently discontinued.**

•Monthly Outcome questionnaires to be completed within 2 weeks of completion of 1st, 2nd and 3rd month's treatment

••Randomisation must be completed within 2 weeks of confirmation and signing of participant eligibility. ↖ To post cycle 2 and 3 trial medication along with the Trial medication diary a week prior the start of cycle ✶To start treatment within 7 days of randomisation.

3. Methods: Interventions

3.1. Intervention description

The intervention arm will receive Ashwagandha (aqueous root extract) at a daily dose of 1000mg in tablet form, taken twice daily (morning and evening) for 3 months (2x(2x250mg) tablets). The control arm will receive placebo tablet indistinguishable from Ashwagandha in appearance, to be taken as per the same regimen. Trial medication will be sent monthly by post with tracked delivery. The courier will confirm that the products were delivered to a member of the correct household and take the name and signature of the recipient. Receipt of the products by trial participant will be confirmed via text and/or phone call from the study team within 2 days.

3.2. Criteria for discontinuing or modifying allocated interventions

Participant will be required to immediately discontinue the trial treatment if any of the following criteria are met:

- Any serious adverse event considered related to the study IMP
- Any ≥ Grade 3 (severe) or higher adverse event considered related to the study IMP
- Pregnancy
- Any medical condition that may jeopardize the participant's safety if he or she continues study treatment
- Use of prohibited medication as per the eligibility criteria and Section 3.4.
- Liver toxicity:
    - ALT or AST >8xULN ○ ALT or AST >5xULN for more than 2 weeks ○ ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

There are no planned intervention modifications in this trial. For all adverse events the PI can interrupt trial medication and reintroduce it once the AE reduces or after careful clinical assessment. If clinically indicated PI can also permanently discontinue the trial medication following an AE. If a participant wishes to discontinue taking trial medication, we will record this and stop sending them the medication. If they agree, we will continue contacting them for follow-up outcomes.

3.3. Strategies to improve adherence to interventions

If participants agree, regular text message and/or email reminders will be offered (no more than weekly) to remind participants to take the tablets.

3.4. Relevant concomitant care permitted or prohibited during trial

There are no documented drug interactions for Ashwagandha. However, on the basis of precaution given the hypothesised actions of the study treatment, the following medications are prohibited: benzodiazepines, anticonvulsants, barbiturates or any other CNS depressants.

There is also a warning in place in regard to potential interactions of the study treatment with the following medicines:

- Immunosuppressants.
- Thyroid hormone.
- Antidiabetic drugs.
- Antihypertensive drugs.
- Aminoglycoside

Participants that are on these medications must be advised of the potential interactions, and their GP's will also be informed. They will be reviewed every month by the investigator during the participation in the trial.

We will recommend that participants inform any health professionals they interact with that they are taking part in this trial if asked about medication or supplement use, and follow their health professional's advice (for example, if their health professional recommends discontinuing the trial medication, then to follow the medical Professional's advice and inform the Trial Manager immediately). We will request that participants do not take other herbal medicines during the trial, and that if they were taking herbal medicines previously, that they stop taking these for the duration of the trial. Herbal medicines are defined as a plant or plant part, or mixture or extract of these, which is taken in medicinal form to improve health, prevent disease, or treat illness. We will suggest that participants do not make other changes to their lifestyle, medication use or supplement use as a result of joining the trial.

3.5. Provisions for post-trial care

We will not offer participants any additional care beyond the stated duration of the intervention period (3 months).

3.6. Ashwagandha and pregnancy

As mentioned above, pregnant or breastfeeding women will not be eligible to take part in the trial, and all participants must agree to adhere to contraception requirements throughout the course of the trial until they are discharged from the trial after their final clinical assessment.

Monthly urine pregnancy test will be done after completing 1st and 2nd month trial medication and a final pregnancy test will be conducted after completing 3rd month trial medication, for all Women of Childbearing Potential, to confirm that no pregnancy occurred during the course of the trial. Investigators may also recommend further pregnancy screening measures at screening or at any other point during the trial if they deem it clinically indicated based on their patient monitoring.

These measures have been included as a precaution given that lack of clinical data confirming the safety of Ashwagandha during pregnancy. However, it is also emphasised that there is no evidence to our knowledge to suggest the trial product will result in harm to mother or foetus during pregnancy. In general usage by Ayurvedic practitioners and as per classical Ayurvedic texts, Ashwagandha is commonly prescribed to women and men for enhancing fertility and can also be prescribed to women to support a healthy pregnancy[17]. Despite these indications, we are not aware of any case reports of harms to foetus or pregnancy with Ashwagandha. A report from Australia noted that there were no gynaecological events in the Database of Adverse Event Notifications (DAEN) associated with its use[18]. A recent systematic review identified 8 clinical studies on the effects of Ashwagandha on the reproductive system[19]. Seven of 8 examined semen quality or sexual function, finding increases in sperm concentration/motility and sexual satisfaction questionnaires, respectively, with no toxic effects reported. One study administered 5g Ashwagandha root powder to 60 infertile men for 3 months, of whom 14% reported a partner's pregnancy within 3 months of treatment, again with no toxic effects noted[20]. To our knowledge, there are no clinical studies examining the safety of Ashwagandha in pregnant women, although varied evidence supports an absence of teratogenic effects within a wide dosage range: firstly, class effects may be inferred based on the herb *Panax Ginseng*, which has similar clinical indications as Ashwagandha, with active compounds (ginsenosides) that are structurally similar to withanolides and thought to exert similar anti-inflammatory and immunomodulatory effects, and for which clinical data supports safety in pregnancy[21]. Secondly, non-clinical reproductive toxicity evidence from rats supports safety for foetus as well as mother up to and including a dose of 2000mg/kg/day (the highest examined in the study, human equivalent: 320mg/kg/day, or ~16g for a 50kg human, substantially beyond the 1g/day proposed in our study)[22]. Another study demonstrated improved reproductive outcomes (reduced foetal loss) among reproductively-impaired mice supplemented with Ashwagandha compared to a control diet[23], supporting clinical claims of its positive effects on female fertility.

4. Methods: Outcomes and follow-up

4.1. Trial outcomes

4.1.1. Primary outcome measure

Self-reported functional status measured using the Post-COVID-19 Functional Status Scale (PCFS), at 3 months[24]. Functional status is a key patient-centred indicator which measures the extent to which a condition limits a person's ability to conduct their usual activities. The PCFS has gained widespread popularity as a tool for measuring self-assessed functional status in long COVID in trials and observational studies and has been translated into multiple languages[25–27]. It was based on a similar, widely-used functional scale for stroke patients, and has been validated in long COVID patients[28]. The PCFS asks patients to consider a flow-chart of options that describe the extent of limitations to their daily activities over the past week. Based on the flow chart, they assign themselves to a grade between 0 (no functional limitations) to 4 (severe functional limitations)..

4.1.2. Secondary outcome measures

i) Quality of life by PROMIS 29+2 summary score, ii) Self-reported fatigue, pain, sleep, anxiety, depression and social, physical and cognitive function by PROMIS 29+2 individual dimensions, iii) Self-reported breathlessness by modified MRC Dyspnoea Scale, iv) Health utility by EQ 5D-5L utility score, v) Work status and productivity, vi) Other self-reported symptoms, vii) adverse events. Outcomes domains were selected to cover the most relevant key indicators for patients and policy makers as well as the most common symptoms of long COVID. Outcome questionnaire instruments were chosen following thorough review of the literature and other ongoing studies, on the basis of wide use/validation, short length (to reduce participant burden), and relevance for this study population (ideally used successfully in long COVID patients before).

4.2. Follow-up for trial outcomes

Follow-up will be through a brief monthly online or postal survey of self-reported functional status, alongside secondary outcome measures such as quality of life, fatigue, breathlessness, pain, mental health, sleep quality, work status, and other symptoms, and brief questions on intervention adherence.

Participants will be followed-up for 3 months (i.e., end of month 1, end of month 2, end of month 3). To be valid, monthly case report forms should be received within 2 weeks of the target completion date (but ideally as close to the target date as possible). Automated email

or text reminders will be sent as per participant preference. In case participants are unable or unwilling to complete surveys online, paper questionnaires in pre-paid return envelopes will be posted each month along with the supplement/placebo packages. A participant would not be contacted to remind them to complete the trial questionnaires more than 3 times. Their nominated contact would only be used as an emergency contact to check the welfare of the participant, and not as a reminder for the participant to complete questionnaires.

4.3. Clinical monitoring

The investigator's clinical team will assess all participants at least monthly and conduct symptom-guided assessment as described in NICE Long Covid guidelines. Assessments will take place at end of 30 days (±3 days, 1st interim assessment), 60 days (±3 days, 2nd interim assessment) and 91 days (final end of trial assessment) since treatment initiation. At each assessment, they will actively elicit the participant's history related to a) any worsening of their long covid, b) exacerbation of any other pre-existing conditions, and c) any side effects that might be related to the drug (including AE/SAE assessment if applicable). To guide assessment of c), we will provide the clinical teams with full list of possible of side effects that have been observed for the trial product (regardless of whether causally attributed). Monthly assessments could be conducted remotely or in-person, as per preference of the investigator or participant. Following the initial assessment, further in-person follow-up including any indicated tests and investigations will be sought if needed based on participant's symptom assessment, and as guided by relevant local and national guidelines. In particular we'll highlight the following areas of assessment: cardiac chest pain, symptoms suggestive of liver or kidney problems, and worsening of psychiatric symptoms. For example, if the investigator notes any symptoms suggestive of a cardiac condition, this might trigger further investigation via X-ray and ECG, while signs of worsening psychiatric symptoms might trigger a psychiatric assessment using relevant validated tool. Any symptoms requiring urgent follow-up would be referred directly to A&E as per usual.

In addition to these monthly clinical assessments, liver function tests (AST, ALT and bilirubin) will be conducted at 30 days (i.e., along with first interim clinical monitoring assessment) and 91 days (i.e., at the end of trial assessment). The test at 30 days is intended to check for any early acute liver toxicity associated with the trial medication (if there is any abnormality noted, participants will be assessed on-site), while the test at 91 days intended to assess for any longer-term effects associated with cumulative build-up of the product in the system. Additional liver function tests could be ordered by the study investigator at any point as

deemed clinically indicated for the patient. Our rationale for this approach is to balance the relatively low risks associated with the trial medication against the potentially moderate risk involved with exposing participants to un-indicated in-person clinical assessments in the context of ongoing COVID-19 transmission. All WOCBP will have to complete a Urine pregnancy test monthly during the trial These tests will be done after completing 1st and 2nd month of trial treatment, and after completing 3rd month's treatment at the final end of study assessment, to confirm that no pregnancies occurred during the trial treatment phase (further detail on Ashwagandha in pregnancy given in section 3.6). Additional urine pregnancy test could be ordered by the study investigator at any if clinically indicated for the patient.

4.3.1. Arrangements for collection, use and destruction of human tissue samples

Blood sample collection for Liver Function Tests will be organised by the study investigator's team and will be conducted as per the clinic trial site's usual NHS testing arrangements. The clinical trial site's Research staff or Phlebotomist will draw approximately 5 ml (1 teaspoon) of venous blood from participant's arm in a gold top blood collection bottle. This blood sample will then be sent to the site's NHS testing laboratory for analysis. After the blood has been analysed, the laboratory will destroy the blood sample following their standard policy for human tissue destruction.

Urine pregnancy testing will be conducted either by the investigator's team when the participant visits the clinical trial site, or by the participant at home. If the urine pregnancy test is conducted in the clinical trial site, then the test result will be analysed and documented by the Research Nurse or delegated individual performing urine pregnancy test and urine sample will be disposed by the clinical trial site's staff following the site's human tissue disposal protocol.
If the test is being conducted at home, the participant will be sent urine pregnancy kit to their home address and will be provided instruction on conducting the test. They will be asked to report their test results to their study Doctor or Research Nurse for documentation. They will be asked to dispose of the urine sample appropriately in the toilet avoiding handling (contact) by other individuals.

4.4. Plans to promote participant retention and complete follow-up

Automated email or text reminders will be sent as per participant preference. If participants fail to respond two months in a row, follow-ups call will be made to them (no more than 3 times) to ascertain participation status in the trial (including vital status).

4.5. Participant discharge from trial

Participants will be discharged from the trial after study investigator has conducted the final end-of-trial monitoring assessment at 91 days since treatment initiation (or within the allotted time window for safety monitoring of 7 days from target date). Final assessment must take place at least 24 hours after the last dose of the treatment was taken, to allow time for systemic exposure to end. This is based on five times the estimated elimination half-life for the product (11.4 hours), plus a conservative additional 12 hours to ensure that no residual systemic exposure remains. Final safety monitoring assessment, AE/SAE recording, contraception requirements, and final pregnancy test will all be conducted at least 24 hours post-completion of trial treatment.

4.6. End of the study

The end of the study is defined as the date of completion of follow-up monitoring of the last participant in the trial. The end of the study will be notified to the relevant review bodies (REC and MHRA) within 90 days as per guidelines.
The trial may also end early if any of the trial termination criteria are met.

Trial termination criteria include:

- If the incidence or severity of AEs in the trial indicate a potential health hazard to participants taking part in the trial.
- If any information leads to conclude that the benefit/risk ratio of the clinical trial is negative.

5. Assignment of interventions: Allocation

5.1. Randomisation

Blinded web-based randomisation in 1:1 ratio after initial consent. Block randomisation (randomly permutated blocks) with varying block size will be used to ensure balance throughout the recruitment period. We will plan to randomise all eligible participants

individually, although after 300 participants have been recruited we will review whether there is repeated incidence of multiple participants from the same household, and whether any issues arose as a result (e.g., mix-up of trial medication, unblinding). If required at this point we may consider restricting the study to a single participant per household.

5.2. Concealment mechanism

Neither participants nor any staff involved in participant recruitment and consent will be made aware of the participant's randomisation status (before or after randomisation).

5.3. Implementation

Before the start of the trial, a randomisation list will be generated by an unblinded staff member based at LSHTM (who will otherwise not be involved in the study). The list will consist of 2500 Trial IDs (unique 4-digit numbers) and corresponding allocation groups (intervention or placebo) assigned in a 1:1 ratio as per the random permutated block design. The list will be shared with the GMP importation partner (IMP Pharmaceutical Services Ltd.) who will print and attach labels and affix them to the corresponding bottles (3 bottles per Trial ID), before QP release and dispatch of the products (in random arrangement) to LSHTM. The ordered list of Trial IDs (without allocation group information) will be shared with the trial team who will allocate the IDs to participants the order in which they are recruited into the study (following receipt and sign-off of the informed consent form). The trial medication bottle labelled with that participant's Trial ID will be retrieved and dispatched to the participant along with the information booklet.

6. Assignment of interventions: Blinding

6.1. Who will be blinded

Participants, study staff conducting recruitment, participant communications, and collecting outcome information will all be blinded to the participants' assignment status. Only the unblinded staff member based at LSHTM (responsible for generating the randomisation lists and the unblinded statistician) will be aware of the assignment of interventions. The Data Monitoring Committee will conduct unblinded monitoring of SAEs, and can also request unblinded interim analyses of outcomes, which will be conducted by an unblinded statistician (who is not involved in day-to-day running of the trial).

6.2. Procedure for unblinding if needed

In general, there should be no requirement for unblinding of the allocated treatment in this trial. If a participant wishes to withdraw, or a new contraindication to Ashwagandha arises, the withdrawal process will be followed. In exceptional circumstances, the study investigator responsible for a particular participant may need to unblind that participant (e.g., in a clinical emergency where clinical management requires knowledge of which treatment the participant has received). In case of such eventualities, all study investigators will have access to unrestricted and immediate access to break the treatment code via a password-protected online system that allows them access to only the request participant's treatment code. The responsibility to break the treatment code in emergency situations resides solely with the investigator. An electronic logging system will be in place to alert the trial team to all occurrences of unblinding of an investigator so that this can be logged and followed-up appropriately.

At the end of the trial, once the results have been published, we will contact participants with the option to find out which arm they were in during the trial. They can opt out of this by letting us know via email or phone at any point.

7. Investigational medicinal product

7.1. Description of the Investigational Medicinal Product (IMP)

The IMP being evaluated in this trial is an aqueous root extract of Ashwagandha in tablet form, taken at a daily dose of 1000mg (4x 250mg tablets per day). An identical-looking placebo tablet based on microcrystalline cellulose has been chosen to prevent participants' awareness of treatment allocation from affecting their responses to the outcome questionnaires. Medication will be sent by tracked courier to participants on a monthly basis (every 30 days) for three months.

The Ashwagandha and placebo tablets have been specially formulated for this trial by a reputed UK-GMP accredited pharmaceutical company based in India (Archimedis Healthcare Pvt Ltd), following extraction and validation methods described in the Ayurvedic Pharmacopoeia of India Part I Volume VIII[29] (see IMPD for more details).

Both Ashwagandha and placebo are prepared as yellow coloured, circular, biconvex, film coated tablets, 11mm in diameter. Tablets are packaged in 100cc plain white, induction sealed HPDE bottles (120 tablets per bottle i.e., to last for 30 days).

7.2. Justification for use of placebo control

A controlled trial is justified because there is genuine equipoise around the efficacy of Ashwagandha for this indication. Administering a placebo tablet in the control arm of this trial (as opposed to no medication) will enable this trial to isolate the therapeutic effect of the trial medication (Ashwagandha) from the known beneficial effects of being prescribed tablets by a doctor or as part of a research study, thus enabling us to robustly assess the efficacy and safety of the medicinal product for this indication. We did not opt for an “active” control arm (e.g., a different medication) as we did not identify any suitable candidates that are standard of care or with proven efficacy for this indication.

7.3. Selection of dosage and regimen for the trial

Ashwagandha is one of the most widely *Rasayana* (rejuvenator) botanicals in Ayurveda practice[29]. There is no single recommended dose of Ashwagandha extract. It is used for a range of indications including as a treatment for inflammatory or immune conditions (where it can be prescribed at higher doses up to 5g per day), and as a general prophylaxis and tonic (where it is typically prescribed at lower doses 250mg-1000mg per day). The lower end of this dose range is often used when Ashwagandha is given in combination with other Ayurvedic herbs.

Given the novelty of Long COVID and our relatively limited understanding of the condition, dose selection for this trial was based on previous effective uses of Ashwagandha for similar clinical indications, and availability of rigorous safety data. Our proposed dose of 1000mg aqueous extract Ashwagandha per day represents a standard therapeutic dose used in Ayurvedic practice for a range of common symptoms, and is also the dose suggested as part of the Indian national guidelines for Ayurvedic management of Covid-19[30]. To date, there are a few clinical studies of Ashwagandha in COVID-19. One examined the effects of 1000mg daily dose of Ashwagandha water extract for prophylaxis of COVID-19, which although distinct shares several purported mechanisms of action with the present trial, such as via antiinflammatory effects (in particular via cytokine regulation) and promotion of immunehomeostasis (Chopra protocol ref). The other clinical study examined an Ayurvedic combination including 1000mg per day of Ashwagandha for improving recovery from acute COVID-19 infection[31]. Among the 96 enrolled adults, they reported faster recovery in the treatment compared with control arm and found mechanistic support for anti-inflammatory

pathways based on attenuated changes C-reactive protein and interleukin-6 from day 1 to day 7 in the treatment arm. A third non-randomised study examined whether patients who opted for Ayurvedic treatment alone vs allopathic plus Ayurvedic treatment showed better recovery over 2 months[32]. There was no fixed Ayurvedic treatment regimen in the study, but the recommended dose of Ashwagandha if used was 1000mg per day. The authors reported faster symptomatic recovery in the Ayurvedic alone group and identified no adverse events during the study.

Generally, when Ashwagandha is taken for management long term symptoms, treatment can be continued for the length of time that symptoms persist. The 3-month (90 day) duration of treatment in this study was therefore chosen based on the typical duration of Long COVID symptoms observed from patient surveys[33,34].

The safety of the proposed daily dose (1000mg) and duration (90 days) of Ashwagandha used in this study are supported by rigorous safety monitoring data from previous clinical trials (Table 1). In a recent study by Chopra et al, 200 healthy participants (healthcare workers in India) were administered Ashwagandha (1000mg water extract) for 4 months for prevention of COVID-19 infection[35]. There were no clinically significant abnormalities (defined as 1.5 times upper normal limit) noted for eGRF, fasting glucose, TSH or in urinalysis for the 4-month duration of the study. One participant in the Ashwagandha arm was observed to have mildly elevated ALT, which resolved by itself within a week and was judged unlikely to be causally related to Ashwagandha. None of these parameters demonstrated statistically significant change between baseline and end-line in the sample overall. In another study from the US, 66 people with schizophrenia and experiencing symptom exacerbation were randomised to Ashwagandha (1000mg daily dose for 3 months) or placebo, and were closely monitored clinically including for vital signs, ECG and biochemical parameters (liver function, renal function, etc)[36]. No clinically significant abnormalities in any parameters were noted during the follow-up. In a randomised trial of 100 infertile (but otherwise healthy) males, 50 men were administered Ashwagandha (5000mg of root powder, equivalent to 1000mg of aqueous root extract) for 3 months, with no clinical abnormalities noted through clinical monitoring including liver function, fasting glucose, TSH and other biochemical parameters[37]. Further discussion on safety including data from a systematic review of side-effects reported across all clinical trials of Ashwagandha are available in the Investigator's Brochure.

Table 1: Safety of proposed dose and duration on biochemical parameters from previous clinical studies

Study ref	Study summary	Sample	Dose / duration	Clinically significant abnormalities in AG arm during follow-up

				Liver (AST, ALT, bilirubin)	Kidney (eGRF)	Fasting glucose	TSH	Urine analysis
Chopra et al, 2021[35]	Ashwagandha vs hydroxychloroquine to prevent COVID-19 infection	N=400 (200 AG) healthcare workers in India	1000mg daily dose for 4 months	1 abnormal ALT, unlikely related to AG	None.	None.	None.	None.
Chengappa et al, 2018[36]	Ashwagandha vs placebo to treat symptom exacerbatio n in schizophreni a	N=66 (33 AG) patients with schizophrenia in USA	1000mg daily dose for 3 months	None.	None.	None.	None.	None.
Nasimi Doost Azgomi et al, 2018[37]	Ashwagandha vs pentoxifylline to improve sperm parameters	N=100 (50 AG) infertile males	5g raw root material (equivalent to 1000 mg water extract) for 3 months	None.	Not examined.	None.	None.	None.

7.4. IMP labelling, supply and management

Following manufacturing and bottling (with unblinded labels) at the UK-GMP facility in India, all IMPs for this trial will be shipped under GMP-compliant conditions to our designated QP partner company based in the UK (IMP Pharmaceutical Services Ltd). The QP partner company will re-label the products with blinded Annex-13 clinical trial labels (using blackout labels that affix over the original labels and cannot be removed without obscuring the original label). Blinded labelling (i.e., matching blinded Trial ID to intervention or placebo products) will be conducted as per the randomisation list supplied by the trial team, in GMP-compliant labelling facilities. Blinded labelled IMPs will be released by the QP partner and shipped to LSHTM in large batches.

Storage instructions for the product are to keep below 25°C and above freezing, and to protect from moisture. These are conservative guidelines based on the accelerated stability studies which have been conducted on these products (demonstrating stability up to 40°C degrees

Celsius and 75% relative humidity). After being received at LSHTM, the IMP will be stored at room temperature in locked cabinets in a locked office accessible only to the study team. Continuous temperature monitoring via an electronic logging system will be used to ensure the product stays within the recommended temperature range. The trial team based at LSHTM will check the temperature on at least a weekly basis and maintain a temperature log. Any short-term deviations from this range will be quickly dealt with using the room's heating or air conditioning facilitates (although this is not anticipated to occur as LSHTM offices are maintained at room temperature by central heating and cooling systems).

After a participant is randomised and is ready for the IMP to be dispatched, a bottle corresponding to that participants Trial ID will be retrieved from the locked cabinet and packaged into an insulated envelope (jiffy bag) addressed to the participant, along with a letter and medication diary. The products will be collected from LSHTM by the designated courier company or LSHTM trial staff will drop the trial medication pack at the nearest courier collection centre, for next day tracked and signed-for delivery to the participant. After delivery has been confirmed by the courier, we will contact participants within 1-2 days to confirm they have received the product.

Delivery delays up to 5 days from dispatch will be tolerated given that the UK has a generally ambient temperature range and that the IMPs are stable to short-term deviations from ambient range. At 6 days or more from dispatch, the products will be recalled to LSHTM. This duration will also help ensure that participants do not have a substantial gap between treatment months (for integrity of the trial intervention). The second and third months' supply of products will be dispatched 5 days from the preceding treatment month ending, to leave ample time for products to arrive without a treatment gap. There will be no set limit within which the participant has to receive and start taking the medication to continue participating in the trial (the trial will be analysed on an intention-to-treat basis regardless), although we aim for none or minimal possible gap between treatment months. If the initial dispatch has not arrived within 5 days, this will be logged, and a replacement product will be sent as soon as the recall is confirmed. In such situations, this may require us to amend the Trial ID on the label of an unused bottle of IMP, to match that of the participant whose product was lost. This will be done by the unblinded staff member at LSHTM (not otherwise involved in the trial) in secure conditions at LSHTM. We anticipate this to be rare and will log and report any occurrences for monitoring by the sponsor and TSC.

7.5. Administration of trial medication, compliance and accountability

Participants will receive their allocated trial medications through the post and will be asked to take the study medication daily for 30 days, by which the next bottle of trial medication should

have been received which should be started on day 31. This will continue for 3 months until day 90. Ideally there should be no break between treatment periods. However, if for any reason there is a break, participants should simply restart taking the trial medication as soon as possible.

Participants will be asked to take four tablets orally per day. Two should be taken in the morning, and two in the evening (although it is not important to strictly stick to this provided the doses are spread out in the day). Tablets should be swallowed whole and warm water (if available) used to wash them down (following Ayurvedic principles). Participants will be given written instructions on how to take the study medication. At or before the start of each 30-day treatment period, participants will be contacted by phone to confirm receipt of the products and reminded of the day that they are scheduled to start the new medication bottle. They will be asked to report a count of any remaining tablets in the previous bottle and told to dispose of any tablets remaining after day 30 in regular domestic waste. In addition, participants will be sent a medication diary along with each month's treatment which they will be encouraged to fill out to help them keep track of their medication usage. Questions on adherence to the study medication will be collected as part of the monthly follow-up questionnaires. Participants will be asked to refer to their medication diaries to help complete these adherence questions. Participants will also be given the trial's contact email and telephone and asked to contact the team in case of any queries or issues with the trial medication.

8. Data management and confidentiality

8.1. Data management

Completed informed consent forms will be retained by clinical trial sites as per their standard procedures. Data from screening, registration, and follow-up case report forms will be stored on secure servers within LSHTM's secure data centre. Any paper-based case report forms will be stored in locked cabinets at LSHTM. Where data entry is required (i.e., for any sections completed by post or on telephone), entry into the same database (via Redcap forms) will be overseen by the Trial Manager. The database will be developed in a way that flags up unusual data values, allowing participants to be contacted by the trial team via phone if there are large amounts of unusual/missing data. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8.2. Confidentiality

All personal information about potential and enrolled participants will be stored securely at LSHTM in accordance with GDPR following LSHTM's stringent confidentiality guidelines. It will only be accessible to necessary study personnel on a need-to-know basis (for example for conducting participant follow-up and posting trial medications), following relevant consents from participants. Only de-identified variables required for conducting trial analyses will be shared with the study analysts.

9. Statistical Methods

9.1. Statistical analysis

A detailed Statistical Analysis Plan will be developed and signed off before any unblinded analyses are undertaken. The primary analysis (of end-line Post-Covid Functional Scale grade) will be on an intention-to-treat basis using ordinal logistic regression (increasingly popular approach for analysis of ordinal scale data in trials with patient-reported outcomes[38,39]), adjusted for baseline levels of the outcome. Multiple imputation will be used to handle missing data. Secondary analyses will involve limited pre-specified subgroup analyses for gender, ethnicity, symptom severity at enrolment, and symptom duration at enrolment. Secondary outcomes will be analysed by ordinal (for ordered categorical variables), logistic (for binary variables) or linear (for continuous variables) regression, also adjusted for baseline values where applicable.

9.2. Sample size calculation

Published data from an online survey of long COVID patients indicate that patients' grade distribution on the Post-Covid Functional Scale (scale 4 (severe) to 0 (none)) improved from of 3.4, 49.4, 35.1, 7.1 and 5.0% at 3 months to 2.1, 43.9, 35.1, 10.5 and 8.4% at 6 months[25]. If Ashwagandha can improve symptoms to a similar extent at 3 months, this translates to an overall odds ratio of 0.71 on the ordinal logistic regression analysis (with an odds ratio less than one indicating a shift to a lower grade of symptoms). In order to improve symptoms with a more modest odds ratio of 0.75, a sample size of 2500 gives in excess of 90% (or 80% power to detect an even more conservative odds ratio of 0.80). An odds ratio of 0.75 would result in the percentages in each grade (grades 4 to 0) being 2.6, 43.1, 38.8, 9.0 and 6.6% in the Ashwagandha arm at end-line. The primary analysis will include adjustment for the baseline value of the primary outcome scale which is expected to increase the power further.

9.3. Interim analyses

Unblinded interim analysis of adverse events will be undertaken by the independent Data Monitoring Committee (DMC) regularly during the trial to monitor safety of the intervention. Stopping rules (for safety concerns or efficacy) will be pre-defined before the trial commences.

10. Oversight and monitoring

10.1. Trial management

The Trial Management Group (TMG) will be responsible for day-to-day management and decision making for the trial; this will be comprised of the study CI, Trial Manager, and relevant study Co-Is as required. They will meet monthly or more often as required. The Trial Steering Committee (TSC) will be responsible for overall oversight of the trial and key decisions including approval of deviations from protocol; this will be comprised of an independent chair, 2 other independent members, a Co-I from AIIA, the CI and two patient representatives. They will meet by video conference every 3 months during the trial. Both TMG and TSC will be kept blinded to trial results until the trial is completed.

10.2. Institutional responsibilities

The trial will be sponsored and coordinated by LSHTM (CI S Kinra); this will include responsibility for regulatory and ethical approvals, clinical trial site recruitment and oversight, intervention delivery to participants, outcome data collection and analysis, scientific dissemination, and insurance cover. Analyses will be carried out by researchers at LSHTM strictly following the pre-specified analysis plan, and results will be published irrespective of the trial findings.

AIIA (Co-I T Nesari) will provide trial medication Ashwagandha and placebo for the trial, funding for the trial activities (see below), and expert advice on trial design and conduct.

Participant recruitment and clinical monitoring will be through participating clinical trial sites. Each site will have a Principal Investigator (PI) who will be a practising GMC registered doctor. PI will be a lead for that site and take responsibility for all the activities performed by any individuals related to the trial. PI will delegate trial responsibilities to his team. Each site will maintain a delegation log specifying individual role and responsibilities. PI will ensure that he/she and any other clinicians actively involved in screening or managing trial

participants (who will act as Sub Investigators), Research Nurses, Clinical Nurses, Physician Associates, Health Care Assistants or any individual associated with performing studyrelated procedures are ICH-GCP trained and will conduct procedures as per the approved trial protocol. It will be the PI's responsibility to ensure that all procedures from approaching and screening eligible participants, clinical follow up while on trial medication to data collection and entry are conducted following GCP guidelines.

10.3. Composition of the Data Monitoring Committee, its role and reporting structure

An independent DMC comprised of 3 clinical trial experts (external to the study) will be established before the start of the trial. This committee will be primarily responsible for monitoring safety of participants in the trial. They will conduct unblinded analysis of adverse events on a regular basis, detailed in the DMC Charter which will be developed prior to start of recruitment. They will be able to request additional interim analyses with appropriate justification in the interest of participant safety. They will pass any recommendations arising from interim analyses (following pre-specified stopping guidelines) onto the TSC.

10.4. Risk assessment

The LSHTM risk assessment SOP has been used to assess the potential risk of this study. The study is considered low risk. Other elements are relatively low risk: the intervention is a widely used and considered a safe food supplement sold in the UK; the confirmed commitment of the study funders; the remote data collection methods (given the COVID-19 epidemic); the minimal time, financial and psychological burden on participants; and the overall simplicity of the protocol. The main sources of risk are the risk of mild side effects related to the supplement (which might discourage some participants from adhering), general risk of participant loss/withdrawal during the course of the trial, and difficulty recruiting up to the target sample size (which may rely on continued prevalence of long COVID-19 in the UK).

11. Safety reporting

11.1. Definitions

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease
	temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death, • Is life-threatening, • Requires inpatient hospitalisation or prolongation of existing hospitalisation, • Results in persistent or significant disability/incapacity, or • Consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • In the case of any other investigational medicinal product, in the investigator brochure (IB) relating to the trial in question.

11.2. Causality

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related side effects due to the drugs used in this study. To assess the grading and seriousness of symptoms CTCAE version 5.0, 27 Nov 2017 will be used. The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. If any doubt about the causality exists, the Chief Investigator will contact the funding institution (AIIA). In the case of discrepant views on causality between the investigators and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be reported.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

11.3. Reporting procedures

Depending on the nature of the event the reporting procedures below should be followed. Collection of AEs and SAEs will start from the participant consent until the final monitoring assessment. After the end of the AE reporting period, if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to the study treatment, the event should be reported to the sponsor.

11.3.1. Non-serious Adverse Reactions (ARs)/Adverse Events (AEs)

Participants will be provided with the contact details of their investigator and.. will be requested to report any potential adverse reactions/events during their monthly monitoring assessments, though they will also have the option to report them on a rolling basis. Potential adverse events (symptom, location and duration) reported during monthly assessments will be entered into the AE Assessment form, and then passed on to a clinical member of the investigator team for assessment of seriousness and noting any recommendation follow-up/monitoring (if applicable). A report summarising all non-serious AEs will be provided to the Data Monitoring Committee on a three-monthly basis. Symptoms that overlap with symptoms being examined on the CRF will not be considered as AEs (unless considered suitably serious, notable and/or prolonged by the clinical member assessing them).

11.3.2. Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)

Participants will be requested to report all serious events including life-threatening illness, hospitalisation or onset of major disability to the investigator on an ongoing basis, and any not reported will also be picked up in the monthly clinical monitoring assessments. An AE Assessment form will be filled and if judged as serious by the clinical team member, the participant will be followed-up by telephone for further details of the adverse event (so the more detailed SAE section of the AE Assessment form can be completed). Expectedness and causality assessment will be conducted by the designated independent clinician and added to the AE Assessment form. Details of all SAEs will be submitted to the sponsor, TSC and Data

Monitoring Committee. Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. Investigator will report SAEs to the Sponsor within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event, regardless of causality.

11.3.3. Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs (i.e., outcomes occurring at an unexpected level) assigned by the independent clinician as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs. The sponsor (LSHTM) will be informed immediately, review the case, and make the decision whether to unblind and report it to the MHRA. For fatal and life-threatening SUSARs the sponsor should report to the MHRA at least the minimum information as soon as possible and, in any case, no later than seven days after being made aware of the case. For other events, the sponsor should report to MHRA within 14 days. Other relevant forms and information will also be provided. Any additional information requested by MHRA will promptly be submitted by the trial team.

11.3.4. Pregnancy reporting and follow-up

If a female subject or partner of a male subject becomes pregnant during the Treatment Period, they should do the following:

- Pregnant subject should immediately stop taking the trial medication and inform the study doctor as soon as possible.
- Pregnant partners: Inform male subjects study doctor as soon as possible. The male subject who was on trial medication can continue to take the trial medication.

Pregnant subject or partners should also inform their pregnancy care team as soon as possible and follow their recommendations. Our study doctors will be available to discuss with them and their doctors if they would like.

We will ask them to provide some information about this pregnancy so that we can learn more about the safety of Ashwagandha in pregnancy. The PI will provide female participants/partner of participant with another Participant Information Sheet and Informed Consent Form to read and discuss with them, before deciding if they wish to consent to provide this information.

Pregnancy follow-up

If the participant/partner agrees to share their information as part of this study, we will contact them twice by telephone to find out some information about their pregnancy. We will call them once soon after they sign the Informed Consent Form, to ask about the following:

1. Relevant medical history
2. Details of any previous pregnancies, including outcome and any complications
3. Details about your current pregnancy
4. Any medications that you are taking/have taken during your pregnancy

And we will call them again within a month after their due date to ask about the following:

1. The outcome of your pregnancy
2. Details of the birth and delivery.

In addition, we will ask them to notify the research team if they decide to terminate the pregnancy or if they experience a miscarriage.

If they are not reachable by phone, we will write them a text message to say that we called. If we do not hear from them, we will contact them up to three times, and after that we will assume that they do not wish to participate and will not contact them again.

12. Ethics, consent and regulatory issues

12.1. Ethics approval

The Study Coordination Centre shall obtain approval from the NHS Research Ethics Committee (REC), the Health Research Authority (HRA), and the LSHTM Interventions Research Ethics Committee. If any substantial changes to the protocol occur, an amendment will be sought from all of these committees, and from the MHRA, and the changes will not be undertaken until all amendments have been approved.

12.2. Consent

Informed consent to join the study will be obtained prior to the participant undergoing clinical screening assessment by a study investigator (as screening assessments involves clinical interview and medical history, and possible blood tests or other investigations). Informed consent will be sought only after the Participant Information Sheet has been shared, a full explanation has been given by the investigator or member of their clinical team, with

opportunity to ask questions, and time allowed for consideration. Informed consent will then be obtained remotely or in-person, through an online form (with box for the participant to add their free-hand signature) or paper form (which if remote may be posted to be completed by hand and returned in a pre-paid envelope). The research team will not contact any potential participants directly until a participant has signed the Informed Consent Form. Participants who are unable to read the trial materials independently (e.g., if English not their first language or due to a health condition) can still participate if the recruiting Investigator deems them to have fully understood the trial materials during the pre-consent discussion. In this case, the consent form must also be signed by their nominated consultee to confirm full understanding of the content of the consent form.

The Investigator will review all submitted consent forms for completeness, following-up with participants if any errors or concerns are noted, and then counter sign the completed forms. Copies of the fully signed informed consent form will be kept by the sponsor and also sent to the participants with their welcome pack.

In recognition that consent is an ongoing process, participants will be prompted at the beginning of each monthly case report form that by completing the form they are reaffirming their consent to participate in the trial, and to get in touch should they have any concerns.

The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

The CI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

12.3. Indemnity

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

12.4. Sponsor

London School of Hygiene & Tropical Medicine will act as the sponsor for this study.

12.5. Funding

The All India Institute of Ayurveda (AIIA) are funding this study and providing the entire supply of Ashwagandha and placebo tablets.

12.6. Frequency and plans for auditing trial conduct

The study may be subject to auditing by the London School of Hygiene & Tropical Medicine (under their remit as sponsor) and other regulatory bodies, to ensure adherence to GCP.

12.7. Plans for communicating important protocol amendments to relevant parties

(e.g., trial participants, ethical committees)

All protocol amendments will be approved by the TSC and then submitted to the MHRA and to LSHTM, REC and HRA ethics committees for review. Participants will be informed (via email, post or phone) only if the amendment is relevant to them (for example duration or dosage of supplement or frequency of contact), and additional consent will be sought as necessary.

If safety data generated on the first 100-200 participants are supportive, it is our intention to submit a protocol amendment to allow reduced clinical monitoring procedures for this trial, and to then proceed with recruiting the remaining trial participants through a more remote model as originally proposed (V1.0 of the protocol). Similarly, if any potential safety concerns arise from the initial safety monitoring data, we may submit a protocol amendment for increased clinical monitoring procedures based on discussion with relevant data monitoring/ethics committees and MHRA.

13. Other trial information

13.1. Dissemination plans

Primary study results will be dissemination via a peer-reviewed publication in an open-access high-impact journal, as soon as possible after trial databases are locked. Following this, press releases and other public statements may be made. Additional publications arising from the trial (secondary analyses etc) will also be published in peer-reviewed journals. At the end of the trial, once the results have been published, we will contact participants to inform them of the results of the trial. They can opt out of this by letting us know via email or phone at any point.

13.2. Publication policy

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Co-Investigators, trial statistician and trial coordinator. Members of the TSC and the DMC will be listed, and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

13.3. Authors' information

This protocol was developed by the following investigators who are responsible for the development of, and agreeing to, the final protocol. Subsequent changes to the final protocol will require the agreement of the TSC.

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