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Participant Information Sheet

Ayurveda for Promoting Recovery In Long COVID Trial

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

We would like to invite you to take part in the above research study. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and family. If there is anything that is not clear or if you would like more information, then please ask a member of the study team for more information. One of our team members will go through this information sheet with you. Joining the study is entirely up to you.

What is the purpose of the study?

Millions of people in the UK have been infected with COVID-19. Studies suggest that up to 1 in 5 people infected with COVID-19 continue to experience long term symptoms such as fatigue, brain fog and muscle pain, for months after their initial infection; a condition commonly known as 'Long COVID'.

Currently there is no established treatment for Long COVID. Researchers at the London School of Hygiene & Tropical Medicine (LSHTM) are conducting a clinical trial to assess whether Ashwagandha, a traditional Indian herbal medicine, can promote recovery from Long COVID.

What is Ashwagandha?

Ashwagandha is a popular form of traditional Indian 'Ayurvedic' medicine that comes from the roots of a plant called 'Withania somnifera'. Previous studies suggest it might improve vitality and muscle strength, reduce anxiety, and improve sleep, which are all common long-term symptoms following COVID-19 infection. This points to Ashwagandha as a potential therapy to promote recovery among people suffering from Long COVID.

Trial Design

In this study we are trying to determine whether Ashwagandha tablets, if taken twice daily for 3 months, can improve functional status, quality of life and alleviate symptoms in UK adults suffering from long-term symptoms of COVID-19. This is a randomised double-blind placebo-controlled study. This means that participants are randomly assigned to receive either Ashwagandha or placebo tablets and neither the participants nor the study team will know which treatment they are receiving.

Who is being invited to take part?

For this study, we are recruiting adults (aged 18 and over) living in the UK who have been diagnosed with Long COVID (as per the NHS Guidelines) by their doctor, and who find that this condition is affecting their ability to carry out their day-to-day activities. We plan to recruit up to 2500 adults to participate in the study.

Do I have to take part?

No. Participation in this study is completely voluntary. It is up to you to decide whether to take part after you have read this information sheet and discussed with friends and family. If needed you can also discuss with your doctor, nurse, and the research team. If you decide not to participate, your doctor will still care for you and your decision will not affect the quality of care you receive.

What will happen to me if I take part?

If you take part, you will be randomly assigned to one of the two treatment options

- Treatment 1: Ashwagandha tablets (trial medication)
- Treatment 2: Placebo tablets (tablets that look exactly like Ashwagandha but do not contain any active substance).

As mentioned before, this study will be *randomised* and *double blind*. This means that you are randomly assigned to either treatment, and that neither you nor the study team will know which treatment you are receiving. However, if required for reasons related to a medical emergency, your doctor can request to find out which treatment you are taking (i.e., Ashwagandha or placebo tablets). If this happens, you may not be able continue participating the trial.

During the study, interactions with the study team i.e., the doctor, the nurse or the research team, will occur remotely (either online, via phone, or via pre-paid postage) or in-person when you visit your study doctor.

What will I have to do?

If you would like to take part in this study, you will need to inform the study doctor who invited you, who will arrange a time to speak with you about the trial. If you choose to join the trial, you will need to complete the following steps:

Step 1: Informed consent

After reading this information sheet and discussing the study with your study doctor, you will be asked to sign an Informed Consent Form (either in-person or online), confirming your willingness to participate in the study. If you are not able to give your consent in-person or online, we can send you a paper copy of the form by post with a prepaid envelope for you to sign and post back to us.

After signing the Informed Consent Form (ICF) you will be registered and allocated a unique Trial ID number. Your medical and trial data will be collected using this unique Trial ID number. Your identifiable data such as your name and contact details will be only used to contact you during the trial and to send trial medication to your home address.

Step 2: Eligibility screening

Once registered, the next stage will be the 'eligibility screening'. In this stage, a study doctor will assess your medical records and health status to confirm that it is safe for you to take part in the study. It's possible that after this stage you will not be able to continue in the study, which your study doctor will discuss with you.

Your study doctor will arrange a time to meet you (either in person at their clinic or by phone call/video call). They will take your medical history, assess your current symptoms and medications, and if required may conduct a physical examination and record your temperature, blood pressure, heart rate etc.

The study doctor will also check your liver function. For this you will need to do a blood test, which will involve giving around 5ml (approximately 1 teaspoon) of blood. Or, if you have done a blood test for liver function recently (within the past 3 months before starting trial medication), then these results can be considered and you will not need to repeat the blood test before you start taking trial medication. Any participants whose liver function test results are abnormal will not be eligible to take part in the trial. We will ask permission to inform your registered GP about this abnormal test result, so that they can follow-up as necessary.

All women of childbearing potential (more detail and definition below) will be asked to take a urine pregnancy test to ensure they are not pregnant.

Step 3: Baseline questionnaire

All eligible participants will be asked to complete a baseline questionnaire which will be sent to you online or by post. It will include questions about your background and health. It should take around 15-20 minutes to complete the questionnaire.

Step 4: Receiving trial medication

After completing the baseline questionnaire, you will be randomly assigned to receive either Ashwagandha or Placebo tablets. In the next few days, trial team will send you the first months' medication via post, along with a copy of this information sheet, a welcome letter, a Trial Card with a 24x7 emergency contact number, and a medication diary to help you keep track of your medication use. We will call you to confirm you have received the medication and answer any queries you may have. We will also send a letter to your GP (if different from your study doctor) to inform them that you are taking part in the trial.

Each month we will send you the trial medication for the next month in a similar way. You will receive trial medication by post 3 times in total (i.e., once for each month of the trial). You should take 2 tablets every morning, and 2 tablets every evening, i.e., a total of 4 tablets per day, with a glass of warm water. There will be enough tablets in each bottle for 30 days.

Step 5: Monthly follow-up and tests

At the end of each month of taking the trial medication, you will be sent an online or postal questionnaire to complete. This will cover: your ability to conduct day-to-day tasks, your quality of life, and any symptoms experienced (such as fatigue, breathlessness, mental health problems). It will take approximately 15-20 minutes to complete. The questionnaires must be completed with 2 weeks of finishing the previous month's trial medication. If we do not receive completed questionnaires, then after a week we will send a reminder by email, text or phone call as per your preference (not more than 3 times).

Additionally, your study doctor's team will check in with you after each month of taking trial medication (by phone or in-person) to see how you are finding the medication, to monitor side effects if any, and to conduct a brief medical assessment regarding safety of trial medication. You will also be able to contact the trial team at any point should you have concerns about the trial medication.

After one month and after three months of trial medication, you will be asked to do a repeat blood test to assess your liver function to confirm that the medication is not having any harmful effects on your liver.

If you are a woman of childbearing potential (see more detail and definition below), you will additionally have to take a pregnancy test at the end of each month of trial medication, to confirm you have not become pregnant during the trial.

Step 6: End of the trial

At least one day after you have completed your three-month course of trial medication, you will be assessed by your study doctor (by phone or in-person) to confirm you can be discharged from the study. This means that there is no reason to suspect any safety concerns from the trial medication, and no need for any further investigations, assessment or follow up in relation to the trial.

Summary of the activities conducted each month during the trial

Trial activity	Pre-trial (screening)	End of month 1	End of month 2	End of month 3 (end of trial)
Informed consent	✓			
Clinical assessment by study doctor	✓	✓	✓	✓
Complete online/ postal questionnaire	✓	✓	✓	✓
Liver function blood test	✓	✓		✓
Urine pregnancy test (if applicable)	✓	✓	✓	✓
Trial medication		Taken daily (2 in morning, 2 in evening)		

Arrangements for the collection, analysis, storage and disposal of blood and urine sample

Blood tests:

Blood tests for this study will be organised by your study doctor. Each blood test will involve taking approximately 5 ml (1 tsp) of blood from one of the veins in your arm by a trained Phlebotomist or a Research staff. This blood will be sent to the 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 tests:

Urine pregnancy tests may be conducted at home or in your study doctor's clinic. If the urine pregnancy test is conducted in the doctor's clinic, then the test result will be analysed and documented by the Research Nurse or individual performing urine pregnancy test, and the urine sample will be disposed by clinic staff following their local human tissue disposal protocol.

If you are sent a urine pregnancy test kit to conduct at home, you will be provided instruction on conducting the test and will be asked to report your test results to your Study Doctor or Research Nurse. You will be asked to dispose of the urine sample appropriately in the toilet avoiding handling (contact) by other individuals.

Contraception requirement while participating in the trial

The safety of the trial medication for developing foetuses is not yet known. Therefore, it is required that participants in this trial take measures to prevent pregnancy from occurring. Any people intending to become pregnant during the trial, or who are unwilling to adhere to the required contraception measures, will not be eligible to participate.

Contraception requirements for each of the following groups of participants are outline below:

Group and definition	Contraception requirement
Women of childbearing potential (WOCBP) *defined as all women who are: "fertile, following menarche (first period) and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy"*	At least ONE of the following: - Taking combined hormonal contraception ("the pill") or progestogen-only hormonal contraception ("minipill") - Intrauterine device ("the coil") or intrauterine hormone-releasing system - Bilateral tubal occlusion (female sterilisation) - Vasectomised partner - Condom use or sexual abstinence (defined as "refraining from heterosexual intercourse") during the entire period of risk associated with the study treatments.
Women who do not meet the above definition for WOCBP, including all post-menopausal women. *A postmenopausal state is defined as no menses (period) for 12 months without an alternative medical cause.*	No contraception requirement.
Men aged 18 and above *(all)*	- Condom use during the entire period of risk associated with the study treatments.

Any failure to adhere to the agreed contraception method must be reported to the study team (doctor, nurse, or trial manager) immediately.

What will happen to participants or partners of participants who become pregnant while they or their partners are taking trial medication?

The trial medication, Ashwagandha, is widely used in many countries, although its safety for developing foetuses has not been researched. There are no known reports of harm to a foetus arising because a parent took Ashwagandha during pregnancy. However, as a precaution, it is important to avoid you or your partner becoming pregnant while taking this trial medication. If you or your partner do become pregnant during the trial, you or your partner should do the following:

- Pregnant participants: Immediately stop taking the trial medication and inform your study doctor as soon as possible.
- Pregnant partners: Inform your study doctor as soon as possible. The participant who was on trial medication can continue taking the trial medication.

You should also inform your pregnancy care team as soon as possible and follow their recommendations. Our study doctors will be available to discuss with you and your doctors if you would like.

We will ask to collect some information about this pregnancy so that we can learn more about the safety of Ashwagandha in pregnancy. We will provide you/your partner with another Participant Information Sheet and Informed Consent Form to read and consider, before deciding if you wish to provide this information.

What are the possible risks and disadvantages?

COVID-19 can have long term negative impacts on patients' quality of life and ability to carry out their normal lives. The potential benefit of Ashwagandha for promoting recovery from COVID-19 has not been proven and should not be relied upon, and you should also follow any advice given by your doctor as you normally would.

Ashwagandha is considered a safe herbal medication which is widely used in India and globally. However as with all medications, there is a possibility that some side effects may occur.

Common side effects

The below list of common mild side effects were reported by between 1 in 100 and 3 in 100 people taking Ashwagandha in previous studies. It should be noted that most studies did not report whether these side effects were related to the Ashwagandha or not, and a similar proportion of people taking placebo tablets also reported these side effects.

- Nausea
- Diarrhoea
- Feeling sleepy

Uncommon side effects

The below list of uncommon mild side effects were reported by between 1 in 100 and 1 in 1000 people taking Ashwagandha in previous studies. It should be noted that most studies

did not report whether these side effects were related to the Ashwagandha or not, and a similar proportion of people taking placebo tablets also reported these side effects.

- Headache
- Rash
- Abdominal pain
- Cough and or cold
- Indigestion
- Dry mouth
- Fever
- Hyperacidity
- Weight gain
- Vivid dreams
- Joint stiffness

Serious side effects

Previous research studies on Ashwagandha have not reported any serious side effects that were related to Ashwagandha. However very rarely, Ashwagandha use has been associated with liver injury. All patients recovered after stopping the medication. This is considered as very rare, as it has been observed in fewer than 1 in 10,000 people taking Ashwagandha.

Allergies

There is a small risk of allergic reactions to Ashwagandha and anyone with a history of allergic reaction to Ashwagandha should not take part.

What to do if you experience side effects

If you experience any unusual symptoms during the trial, you should contact your study Doctor on [recruiting site phone number]. If it is an emergency, you should visit your nearest Accident and Emergency (A&E) centre as you usually would and inform your study doctor as soon as possible.

If another medical doctor treating you requires information about your participation in the trial on an emergency basis, they should contact us on the emergency 24x7 number provided on your recruitment card. If requested, we will provide them with information about your participation in the trial. We ask that you carry your recruitment card with you at all times in case it is needed in a medical emergency.

What are the possible benefits?

We cannot promise the study will benefit you directly, but the information we get from the study will help our knowledge and understanding of how to treat long-term symptoms of COVID-19, for which there is currently no proven medical treatment or cure.

Can I get hold of the trial medication after the trial?

The Ashwagandha and Placebo tablets being used in this trial have been specially formulated and manufactured in accordance with UK medicines regulations by a reputed pharmaceutical company in India. After you complete your 90 days of treatment as part of this trial, no further medication will be made available to you. This formulation of Ashwagandha is not currently available for sale in the UK. However, at your request we could let you know if this medication becomes available in future.

What if something goes wrong?

If you have a concern about any aspect of this study, you should contact your study doctor's team on [recruiting site phone number], or the Trial Manager (email: april@lshtm.ac.uk, or phone: +44 (0)7510 382984) who will try their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting the Sponsor's representative Patricia Henley, Head of Research Governance and Integrity at the London School of Hygiene & Tropical Medicine (LSHTM), at RGIO@lshtm.ac.uk or +44 (0)207 927 2626. You could also contact your local NHS Patient Advice and Liaison Services (PALS) on [insert details of local PALS for this recruiting site].

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the clinical site that recruited you or against LSHTM, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). LSHTM also holds insurance policies that provide cover if you are harmed, even if there was no negligence by the clinical or research team. In such circumstances you may be eligible to claim compensation against LSHTM. For more information you can contact the Trial Manager or Sponsor's representative using the contact details provided above.

Can I change my mind about taking part?

Yes. You can withdraw from the study at any time, with no requirement to give a reason. However, you should be aware that, if you agree to take part in the study, it will not be possible to remove your details from our database later (following UK regulations on drug trials).

How will we use information about you?

We will need to use information from you and your study doctor for this research project.

This information will include your:

- Name
- Residential address
- Email address

- Telephone number

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by sending an email to DPO@lshtm.ac.uk
- by sending an email to the research team at april@lshtm.ac.uk
- by ringing the research team on 07510 382 984.

What will happen to the results of this study?

The study results will be published in a medical journal so that other doctors and policymakers can learn from them. Findings may also be featured in newspapers or other media outlets. No personal information about you will be included in the study reports and will write our reports in a way that no-one can work out that you took part in the study.

Who is organising and funding this study?

London School of Hygiene & Tropical Medicine is the sponsor for the research, and they have full responsibility for the project including the collection, storage and analysis of your data, and will act as the Data Controller for the study. This means that we are responsible for looking after your information and using it properly.

The All India Institute of Ayurveda (a research institute in India funded by the Government of India), is providing the standardised, high quality Ashwagandha and placebo tablets for this trial. The Ministry of AYUSH, Government of India, is funding the trial.

Who has reviewed this study?

All research involving human participants is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the NHS Research Ethics Committee (REC) and Health Research Authority (HRA) (ref: 22/WA/0157) and The London School of Hygiene & Tropical Medicine Research Ethics Committee (REF: 28143). Use of Ashwagandha in this clinical trial has been approved by the UK Medicines and Healthcare Regulatory Agency (MHRA).

Further information and contact details

Thank you for taking time to read this information sheet. If you think you are interested in taking part in the study, please read and sign the Informed Consent Form.

If you would like any further information, please contact the trial team who can answer any questions you may have about the study.

Contact details:

Recruiting Site	Principle investigator: Dr XX Contact: XX
Central trial team	Dr Manisha Joshi (Registered Clinical Research Practitioner and Ayurvedic Physician) Clinical Trial Manager for APRIL London School of Hygiene & Tropical Medicine Keppel Street, London WC1E, 7HT Email: april@lshtm.ac.uk Phone: 07510 382 984, Mon to Fri 10:00 to 16:00