

Colchicine for Long COVID trial

Study Title: Colchicine to Reduce Coronavirus Disease-19 Related Inflammation and Cardiovascular complications in High-Risk Patients Post-Acute Infection With SARS-COV-2(CTRI/2021/11/038234)

Sponsor: The George Institute for Global Health, India

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Background: Long COVID is a new condition affecting millions of individuals worldwide. Information about its incidence, prevalence, pathophysiology, and prognosis is emerging at a rapid pace. Long COVID manifests with myriad of symptoms involving several organs and systems. Commonly reported symptoms are fatigue, memory loss and depression. Currently there are no known medications available to prevent or treat Long COVID.

Project summary: The primary objective of this study is to assess whether colchicine, a cheap and widely available oral drug, can safely prevent the development and/or progression of long COVID in individuals with persistent symptoms after initial recovery from acute infection with SARS-CoV-2. We will evaluate the effect of this drug on several outcomes of importance to the patients – the main one (primary objective) being distance walked in 6 minutes. The others (secondary objectives) will include assessment of respiratory and psychiatric symptoms, and the effects on inflammation of the heart, by cardiac MRI. Participants will be required to visit the hospital at 12, 26 and 52 weeks after enrolment.

Community engagement activity

The George Institute, India arranged for an informal meeting via Zoom with individuals with Long-COVID with the help of a community representative Ms. Padma Priya. The study materials were shared via the Long COVID patient group on Telegram - a popular messaging platform.

The purpose of the meeting was

1. To get views about the study from individuals with experience of having lived with Long COVID
2. To disseminate information about the trial to maximize opportunities for those meeting the eligibility criteria to participate in the trial
3. To answer any queries related to study

Some questions asked during the discussions

- 1 Can people with pre-existing conditions enrol for this study? What happens if the pre-existing condition is immune system related and they are on immune suppression drugs?

People with pre-existing conditions can enrol in the study if Colchicine does not interact with the participant's treatment. Participants would be asked about their known pre-existing illnesses during the screening phase. Based on the pre-existing disease information, the participant's treatment physician would decide the participant's eligibility for the study. After enrolment, if the participant develops some condition or is on treatment that may interact with Colchicine, the physician may decide to discontinue the trial medication temporarily or permanently. Individuals in immunosuppressed states or on treatments that

can cause immunosuppression will not be enrolled in the trial. Further, any condition that can lead to poor absorption of the trial medication such as chronic diarrhoea or that can delay the excretion of the medicine such as impaired renal or liver function, and then the physician may not enrol the participant into the trial.

2 Do they need to live in same city or town of the activated centres to enrol in the study?

If the participant can visit the clinical site at the time of enrolment and the scheduled visits at the designated clinical sites. In that case, it is not a necessity that the participant is residing in the same city or town to enrol in the trial.

3 How often and what kind of testing do the trial offer?

The testing includes performance-based tests such as the lung function (spirometry) blood test for C-reactive protein and full blood count. In addition, the participants would also undergo a 6-minute walk test. We will also invite a small set of participants for an MRI study of the heart if they are willing. The study will cover the costs of the tests, and the participants do not have to pay anything

4 Will data be available to the participants?

The results will be published in an international scientific journal when the trial is completed. We will also publish a summary in simple language and make it available on our website. If you would like more information about the trial results, including any implications for you, you can contact your treating doctor or a study team member (colchicine@georgeinstitute.org.in).

5 What kind of support system a volunteer can have?

The volunteer can seek medical advice from the physician at the clinical trial site. If you might require a referral to any other specialist doctor, the physician will be able to guide and refer the participants to appropriate facilities. In addition, the study team at the clinical site would be able to connect you to a long COVID support group.

6 How do you plan to manage personal health data of trial participants? How long will data be retained, by whom or how long?

The study does not intend to collect any direct personal identifiers of the participants. Data will be collected in a case report form (CRF) designed for study purposes. The data collected will be identified by a unique numerical ID. So, when we get the data from the clinical site, we will not know who the trial participant is. The collected data is stored in password protected database that is accessible strictly to the research team. All research staff involved in the trial have undergone training on ethics, research integrity, and good research practices. Only data that does not have anything to identify individual participants will be used for analysis. Only the data required to answer research questions are collected in this trial. The George Institute for Global Health may use the data already collected in this study to answer more questions about participants' health and the study medication. These studies may be needed to improve knowledge of how to better care for patients affected by Long COVID.

- 7 Do you have mandatory identification required? will trial participants be forced to enrol in government health ID?

No personal identification will be required to participate in the study. Data collected for research purposes and information collected for clinical care will be de-linked. The trial participants will be identified by a unique ID that is not linked to their identifiers.

- 8 What kind of support (Medical and financial) is available to trial participants who suffer unexpected side effects? does the support available after the trial?

Participation in the trial is at no cost to the participant. All participants in the study will have access to the treating clinician. The study is covered under clinical trials insurance to compensate for any harm due to participation, as per the procedures outlined in the study protocol. In the event of any unexpected side effect that is directly caused due to trial participation, the individual will receive medical care free of cost. Per the trial insurance policy, the participant will also receive monetary compensation for any loss, proportional to age and occupation. These safeguards to protect the trial participant is laid out in ethical and regulatory guidelines at the national level for all clinical trials. The trial treatment is for 6 months. If there is any emerging evidence for longer duration, then the medication can be easily purchased as it is a very inexpensive medication.

- 9 Many women have severe flare ups during their menses. Has that been included in the events of special interest?

This has not been included in the trial. We can add these as separate questionnaires or develop an e-diary to record the symptoms.

- 10 Specific pathway through which you hope this helps to manage Long COVID?

Colchicine modifies the immunological response and reduced inflammatory activity. Since, long COVID is due to immune-mediated inflammation we expect Colchicine may have some benefit. Colchicine has shown benefit in other chronic inflammatory conditions.

- 11 Is 6MWT standardized measure for Long COVID? Long COVID patients can perform 6MWT during the day of visit but PEM is a different matter post 24-72 hrs?

In case the participants experience PEM as a result of the study-related tests or even otherwise, the participants would be managed by the treating physician. The study team will create procedures to be in touch with the participants to provide resolution of the PEM.

- 12 How your previous trial phases influenced the choice of your primary outcome variable?

6 MWT is generic test for functional ability and general fitness. This test also is surrogate (Proxy) measure for cardio-respiratory fitness. Functional limitation could be due to musculoskeletal reasons or deconditioning due to prolonged illness. Since the Long-COVID presents with myriad of constitutional symptoms, 6MWT test is something that captures the overall functional capacity of an individual. However, the trial also captures several measures such as fatigue, depression, and overall quality of life. The interpretation of trial results will be based on all these parameters.

13 Rationale behind the drug intervention for 6 Months?

It is believed that the inflammation triggered by response of the human immune system against the SARS-COV2 virus remains even after the acute infection subsides for a varied duration duration. Emerging evidence is showing that the features of long-COVID can appear for the first time or recur for a long period. The exact upper limit beyond which the physiological changes that cause long-COVID is not known. This is the reason that a 26-week duration has been chosen. This field is evolving and only by studies like this one we will know what is best.

14 Do I need to stop the medication if I have some side effects in the initial days?

The medicinal properties of colchicine are well known. It has been in clinical use since 1500 BC, has been in the market as a pharmaceutical product in use in the current form since the 1950s and has a well-known safety profile. Like all other medications, it has some side-effects which is expected. The side-effects can be mild to severe by nature. The key thing to remember is, we want the beneficial effect to far outweigh the risk of any side-effect. Some side-effects that one may experience in the beginning of the treatment may disappear after a few days. However, decision to stop /wait and watch /continue will be based on a mutual discussion between the participation and the doctor and depends on the severity of the side-effect.