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Symptoms, trajectory, inequalities and management: understanding Long COVID to address and transform existing integrated care pathways

Submission date
16/05/2022

Recruitment status
No longer recruiting

Registration date
30/05/2022

Overall study status
Completed

Last Edited
05/11/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Currently, effective treatments for Long COVID are not defined or well understood and the availability of different treatments can vary based on where you live. The aim of this study is to measure and compare the effectiveness of the current interventions, including MRI scan (Coverscan™) and an enhanced rehabilitation App (Living with COVID Recovery™), used for the treatment of Long COVID, on their own and in combination with drug treatments. The researchers will use this information to develop the most effective treatment pathway. To do that, they will need to collect data from patients with Long COVID about their illness, their treatment, and their progress. Data will be collected from patients' medical records from January 2020 (this is the date COVID-19 was recognised to be circulating in the UK) for up to 1 year after their first clinic appointment. The researchers will also be testing selected drug treatments (for eligible patients who consent to be in the drug arm of the trial) and their effectiveness on Long COVID symptoms and recovery. There is little known about why Long COVID occurs in some patients and not others, and why it is unrelated to the severity of the initial illness. To explore this more, the researchers will be asking participants to also consider giving blood samples to support further research to better understand underlying factors that would identify people most likely to develop Long COVID. This may help to tailor specific interventions earlier in the treatment pathway. The samples would also be used for future research into Long COVID and other emerging public health studies.

Who can participate?
Adults aged 18 years and over who have been referred for their first Long COVID Clinic appointment that is participating in STIMULATE-ICP and meet all eligibility criteria.

What does the study involve?
What happens during the trial depends on which parts the participant chooses to participate in. Participants can choose to participate in all aspects of the trial that they are eligible for, or just the parts of the trial that they have chosen and are eligible for. The different groups are as

follows:
Group 1: Data collection + drug trial + research blood sampling
Group 2: Data collection + drug trial
Group 3: Data collection + research blood sampling
Group 4: Data collection only
The clinic study team will check that participants are eligible. They will do this by asking questions about medical history and medication use. During the trial there will be three data collection timepoints; the first is the Long COVID clinic appointment, or the first visit to the study team. The second is at 12 weeks and the third at 24 weeks. The first and second visits will be conducted by the clinic study team. The researchers would prefer the second visit to be face-to-face, however, participants have the option to complete the visit online or by phone, some of the questionnaires can be returned to the Lancashire CTU by a postage-paid envelope. The third visit will be followed up by Lancashire CTU and participants will also receive a call from the local study team to follow up on any adverse events participants may have been experiencing. This visit can be completed online, by phone or by returning the questionnaires to Lancashire CTU in a postage-paid envelope.

What are the possible benefits and risks of participating?
It is possible that participants may not benefit from taking part in this trial. The results of the trial may also help in finding new treatments for Long COVID in the future. As with any medicine, side effects may occur with the study drug treatments, although not everybody will get them. The risks and most common side effects are listed below: loratadine; at the recommended dose of 10 mg daily, side effects with loratadine are minor and include drowsiness, headache, increased appetite, and insomnia. Famotidine: at the recommended dose of 40 mg daily, the most common side effects include headache, dizziness, diarrhoea, constipation, and agitation (in less than 1% of patients). Colchicine: at the recommended dose of 500 micrograms twice a day, the most common side effects include nausea (feeling sick), abdominal (stomach) discomfort and /or diarrhoea. These as usually ‘mild, transient, and reversible’ when the colchicine dose is lowered or stopped. Other side effects observed at higher doses than those used in this trial are rare but can include a decrease in blood cells (agranulocytosis, aplastic anaemia, thrombocytopenia) which can cause fever, infections, sore mouth or throat, bleeding, bruising or tiredness. Other rare side effects include impaired nerve function, causing a sunburn sensation, weakness, tingling or numbness (peripheral neuropathy), impairment of liver or kidneys, hair loss, rash, itch, and painful or weak muscles (myopathy), absence or discomfort of menstrual periods (amenorrhoea, dysmenorrhoea) or reduced ability to produce sperm resulting in low (oligospermia) or zero (azoospermia) sperm count. Rivaroxaban: at the recommended dose of 10 mg daily the most common side effects include nausea, vomiting, tiredness and lack of energy, shortness of breath, heart palpitations and pale skin (this could be a sign of anaemia), feeling dizzy or lightheaded, a mild rash. Rivaroxaban is not recommended if participants are at risk of bleeding, have kidney impairment, uncontrolled high blood pressure, or have gastrointestinal diseases such as an ulcer or inflammatory bowel disease or acid reflux, oesophagitis, and gastritis. Rivaroxaban will not be prescribed if participants have recently undergone prosthetic heart or aortic valve replacement. Most of the side effects are usually minor and resolve very quickly.

Where is the study run from?
Lancashire Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
December 2021 to August 2025

Who is funding the study?
1. National Institute for Health Research (NIHR) (UK)
2. UK Research and Innovation (UK)
3. Perspectum (UK)

Who is the main contact?
Prof. Amitava Banerjee
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Contact information

Type(s)
Principal investigator

Contact name
Prof Amitava Banerjee

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006598-47

Integrated Research Application System (IRAS)
1004698

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 51981, IRAS 1004698

Study information

Scientific Title
STIMULATE-ICP: A pragmatic, multi-centre, cluster randomised trial of an integrated care pathway with a nested, Phase III, open-label, adaptive platform randomised drug trial in individuals with Long COVID

Acronym

STIMULATE_ICP

Study objectives
The STIMULATE-ICP trial is testing the hypothesis that an Integrated Care Pathway for Long COVID is more effective than Usual Care at improving the most common symptom of fatigue. It is hypothesised that drug treatments in Long COVID may significantly improve symptoms and physical function through different mechanisms of action. Researchers have designed an adaptive, platform clinical trial within STIMULATE-ICP to robustly test the efficacy of drugs in Long COVID. They will start with loratadine plus famotidine, colchicine and rivaroxaban and continue to add/remove drugs according to emerging preliminary data in Long COVID and as approved by the Independent Data Monitoring Committee (IDMC), Trial Steering Committee (TSC) and the Funder (NIHR). Estimating the individual effect size of these drugs on fatigue is complex, as extrapolating preliminary data to the larger patient cohort is difficult. It is hypothesised that Long COVID patients who experience symptoms may gain the most benefit from the trial drugs, but in the absence of detailed pathophysiological data for Long COVID, the researchers are open to the possibility of differential effects of these drugs in different sub-groups.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/01/2022, South Central - Berkshire Research Ethics Committee (Bristol REC Centre, Temple Quay House, 2 The Square, Temple Quay, Bristol, BS1 6PN, UK; +44 (0)207 104 8178; berkshire.rec@hra.nhs.uk), ref: 21/SC/0416

Study design
Randomized; Both; Design type: Treatment, Diagnosis, Process of Care, Drug, Device, Imaging, Complex Intervention, Management of Care, Rehabilitation, Validation of outcome measures

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
1. Loratadine + famotidine plus usual care: loratadine 10 mg tablet once a day swallowed whole with water every morning and famotidine 40 mg tablet once a day swallowed whole with water every morning. The treatment duration is 84 days
2. Colchicine plus usual care: colchicine 500 mcg tablet, one tablet twice a day swallowed whole with water (12 hours apart). The treatment duration is 84 days
3. Rivaroxaban plus usual care: rivaroxaban 10 mg tablet once a day swallowed whole with water every morning. The treatment duration is 84 days
4. No-drug (usual care): as per usual standard of care.

Follow-up:
All participants irrespective of the nested drug trial will receive 12-and 24-week (after initial Long COVID Clinic Appointment) follow-ups in accordance with the protocol.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Fatigue measured using the Fatigue Assessment Scale at baseline,12 and 24 weeks

Key secondary outcome(s))
1. Health-related quality of life is measured using the EQ-5D-5L at baseline, 12 and 24 weeks
2. Mental health is measured using the Generalised Anxiety Disorder Assessment (GAD-7) at baseline, 12 and 24 weeks
3. Depression is measured using Patient Health Questionnaire (PHQ-9) at baseline, 12 and 24 weeks
4. Dyspnoea is measured using MRC Dyspnoea Score at baseline, 12 and 24 weeks
5. Cognitive functioning measured using the Perceived Deficit Questionnaire (PDQ-5) at baseline, 12 and 24 weeks
6. Functional Impairment measured using the Work and Social Adjustment Scale (WSAS) (Question 4 from Productivity Cost Questionnaire (iPCQ) for absenteeism and Question 8 from iPCQ for presenteeism added) at baseline, 12 and 24 weeks
7. Health-related quality-of-life measured using the Short Form Questionnaire (SF-12) at baseline, 12 and 24 weeks
8. Cognitive dysfunction measured using the Cognitive Failure Questionnaire (CFQ) if a patient scores 3 or more on PDQ5 (patients receive an email to complete this questionnaire online via a secure password and patient ID number) at baseline, 12 and 24 weeks
9. Organ impairment and healthcare utilisation measured using patient records and the case report form (CRF) at baseline, 12 and 24 weeks
10. Cost-effectiveness of integrated care pathway (ICP) measured using patient records and the case report form (CRF) at baseline, 12 and 24 weeks
11. Process outcomes for different ICP components: whether pre-specified subgroups of patients, either grouped by clinical symptom cluster or imaging findings, benefit from either early investigation with COVERSCAN™, IMPs or rehabilitation, measured through the ICP components including CoverScan and The Living With COVID Recovery App
12. Blood investigations (e.g., genomic, proteomic, metabolomic/lipidomic, functional T cell and live virus neutralisation assays and endocrine analysis) measured using the research blood collected on study at baseline and 12 weeks

Completion date
07/08/2025

Eligibility

Key inclusion criteria
Inclusion criteria for ALL participants
1. Participants capable of giving informed consent

2. Age 18 years and above
3. Clinical parameters; persistent signs and symptoms for a period of 4 weeks or longer in duration post-COVID-19 infection (either by test result or symptomology). Presenting at their first referral first visit to a participating Long COVID clinic pathway.
4. Able to read or understand English or have a relative/family member able to read/understand English to facilitate participation (essential for patient-reported outcome measures at follow-up time points and virtual contact)
5. Not enrolled in any other interventional study where study intervention/activities may affect outcome measures (patients enrolled in purely observational studies can be included)

Additional inclusion criteria for the nested, platform randomised drug trial (to be eligible participants must meet all above criteria and all those below). Note: Potential participants with drug-specific contraindications for any arm, including interactions of pre-prescribed essential medication will be consented for data collection but will be excluded from the drug study.

6. Females of childbearing potential (see definition below) must be willing to use an acceptable effective method of contraception during the treatment with the IMP and for a further 30 days after the last dose. Such methods include:
6.1. Combined (oestrogen and progestogen containing) hormonal contraception:
6.1.1. Oral
6.1.2. Intravaginal
6.1.3. Transdermal
6.2. Progestogen-only hormonal contraception
6.2.1. Oral
6.2.2. Injectable
6.2.3. Implantable
6.3. Intrauterine device (IUD)
6.4. Intrauterine hormone-releasing system (IUS)
6.5. Bilateral tubal occlusion
6.6. Vasectomised partner
6.7. Male or female condom with spermicide
6.8. Cap, diaphragm or sponge with spermicide
6.9. Sexual abstinence; only true abstinence is acceptable i.e. when this is in line with the preferred and usual lifestyle of the participant). (periodic abstinence, declaration of abstinence during exposure to IMP and withdrawal are not accepted methods of contraception).
For the purpose of this trial, a female is considered of childbearing potential i.e. fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without alternative medical cause.
7. Male participants must be willing to use condoms during IMP treatment and for a further 90 days after the last dose of trial IMP to protect their female partner from becoming pregnant
8. Patients on pre-existing treatments for the same drug classes MUST undergo a 7-day washout period before being randomised.
(Patients will be assessed, and if safe to do so, exclude that medication for 7 days, asked if they would be willing to undergo a washout period of at least 7 days before being randomised)

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
1555

Key exclusion criteria
Exclusion criteria for ALL participants:
1. Previously hospitalised for COVID-19 infection
2. Previously referred to a long COVID clinic

Exclusion criteria for nested, adaptive randomised drug trial:
3. Females who are pregnant, planning pregnancy or breastfeeding
4. Known hypersensitivity to any of the study drugs or their excipients
5. Currently taking any of the following drugs: probenecid, sucrafate, isocarboxazid, phenylzine, tranylcypromine of any other CNS depressant (such as diphenhydramine, dextromethorphan, or pseudoephedrine) (contraindications to famotidine/loratadine), amiodarone, aprepitant, atanazavir, atorvostatin, azithromycin, bezafibrate,ciclosporin, ciprofibrate, clarithromycin, cobicistat, croztibib, darunavir, diltiazem, dronedarone, eliglustat, erythromycin, fenobibrate, fluconazole, fluvastatin, fosamprenavir, gemfibrozil, idelalisib, imatibib, isavuconazole, itraconazole, ketoconazole, letermovir, lopinavir, netupitant, nilotinib, posaconazole, pravastatin, ranolazine, ritonavir, rosuvastatin, simvastatin, tipranavir, velpatasvir, vemurafenib, venetoclax, verapamil, voriconazole (contraindications to colchicine), acalabrutinib, aceclofenac, acenocoumarol, alprostadil, alteplase, argatroban, aspirin, axitinib, beniparin, benzydamine, bevacizumab, bismuth, bivalirudin, bosutinib, bromfenac, cabozantinib, cangrelor, caplacizumab, celecoxib, cilostazol, clopidogrel, cobimetinib, dabigatran, dalteparin, danaparoid, dasatinib, dexkeptorofen, diclofenac, dipyridamole, enoxaparin, epoprostenol, eptifibatide, etodolac, etoricoxib, flurbiprofen, heparin, ibrutanib, ibuprofen, iloprost, imatinib, indomethacin, inotersen, ketoprofen, ketorolac, levatinib, mefenamic acid, meloxicam, nabumetone, naproxen, nicotinic acid, nintenanib, parecoxib, pazopanib, phenazone, phenindione, piroxicam, ponatinib, prasugrel, regorafenib, ruxolitinib, sorafenib, streptokinase, sulindac, sunitinib, tenecteplase, tenoxicam, tiaprofenic acid, ticagrelor, tinzaparin, tirofiban, tolfenamic acid, trametinib, traztuzumab emtansine, trprostinil, urokinase, volanesorsen, warfarin (contraindications to rivaroxaban)
6. No history or presenting symptomology suggestive of renal failure/insufficiency (eGFR <30 ml minute) on the basis of blood investigations (eGFR) within the last 6 months and clinical assessment
7. Severe liver dysfunction on the basis of blood investigations within the last 6 months (liver function and coagulation) and clinical assessment

Date of first enrolment
16/06/2022

Date of final enrolment
31/07/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Glenfield Hospital
Groby Road
Leicester
United Kingdom
LE3 9QP

Study participating centre
Liverpool Tier 3 Long COVID Service
Townsend Lane Neighbourhood Health Centre
98 Townsend Ln
Anfield
Liverpool
United Kingdom
L6 0BB

Study participating centre
Princes Park Health Centre
Bentley Rd
Liverpool
United Kingdom
L8 0SY

Study participating centre
University College Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre

Castle Hill Hospital
Castle Road
Cottingham
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HU16 5JQ

Study participating centre
Walton Hospital
Whitecoates Lane
Chesterfield
United Kingdom
S40 3HW

Study participating centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Perspectum

Results and Publications

Individual participant data (IPD) sharing plan
The trial will adhere to the NIHR Open Access Policy regarding accessibility and data sharing. Details of the policy are published and updated on the NIHR website; https://www.nihr.ac.uk /documents/nihr-open-access-policy/28999. The policy does not require that the data must be made open.
Sharing of the trial data must protect the confidentiality and privacy of participants; respect the terms of consent by participants who are involved in the trial; be consistent with relevant legal, ethical and regulatory frameworks; and guard against unreasonable costs.
The release of the anonymized trial data will be subject to a data-sharing agreement between the Sponsor, CI and the third party requesting the data. The integrity of the data must always be preserved, and the agreement should be aligned with the Sponsor and Lancashire CTU SOPs on data sharing.
Further details will be made available at a later date and any requests for data sharing should be made to Denise Forshaw, Deputy Director, Lancashire Clinical Trials Unit (dforshaw@uclan.ac.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/02/2023	16/02/2023	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes