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Therapies for Long COVID

Submission date	Recruitment status	[_] Prospectively registered
09/11/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
24/11/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
09/04/2024	Infections and Infestations	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Some people who have survived COVID-19 infection develop longer-lasting symptoms, known as Long COVID. Many lack support and are given conflicting advice. The study aims to work out which treatments are most likely to benefit people with particular symptoms and test supportive treatments to improve quality of life.

Who can participate?
Participants will be selected from a central database of GP record data hosted by the Medicines and Healthcare Regulatory Authority (MHRA). Participants will be selected if they have had a positive test for COVID-19 and have not been admitted to hospital within 28 days, or if they have not had COVID-19 (the comparison group).

What does the study involve?
Participants will be invited to report symptoms, quality of life and work capability on a digital platform called Atom5TM either through an app, web browser or by telephone. This will be done once a month for 12 months. Those reporting significant symptoms will be contacted by a research nurse for advice and guidance. Some participants will be invited to the BioWear sub-study to provide blood and saliva samples and will be provided with a Garmin wearable device at the University Hospitals Birmingham Clinical Research Facility or at home with a research nurse. These samples will be used to understand the immune mechanisms causing Long COVID symptoms. The final part of the study is a feasibility study of pacing interventions to support people experiencing fatigue and other symptoms from long Covid.

What are the possible benefits and risks of participating?
This study will help the researchers understand people's experiences with COVID-19 and help develop an intervention to support people with Long COVID symptoms. Participants may find it rewarding to take part in research that may help improve healthcare for people who have Long COVID. Those who take part will receive a £10 voucher code after completing the first questionnaire and another £10 voucher code upon completing the final questionnaire at 12 months. Those selected to take part in the BioWear sub-study can keep the Garmin wearable device upon completing the study.
The researchers anticipate minimal risks for participating in this study. However, some of the questionnaires contain sensitive questions which some people may find upsetting, difficult or may lead them to recall challenging moments in their life; for example, questions about anxiety.

Taking part in the study and any answers given in questionnaires will not negatively affect the quality of their treatment, care or legal rights. Participants are free at any point to stop taking part with no explanation required.

Where is the study run from?
The University of Birmingham and University Hospitals Birmingham in partnership with the Clinical Practice Research Datalink and Aparito Ltd (UK)

When is the study starting and how long is it expected to run for?
March 2021 to March 2023

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

Who is the main contact?
Dr Shamil Haroon and Prof. Melanie Calvert
tlcstudy@contacts.bham.ac.uk

Study website
https://www.birmingham.ac.uk/tlc

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
296374

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50336, IRAS 296374

Study information

Scientific Title
Therapies for Long COVID in non-hospitalised individuals: from symptoms, patient-reported outcomes and immunology to targeted therapies (the TLC study)

Acronym
TLC

Study objectives
Individuals with Long COVID experience a wide range of symptoms that can be grouped into specific clusters that may represent different disease phenotypes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/10/2021, Solihull Research Ethics Committee (Equinox House, City Link, Nottingham, NG42 4LA, UK; +44 (0)207 1048191; solihull.rec@hra.nhs.uk), REC ref: 21/WM/0203

Study design
Observational; Design type: Cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See additional files

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

Interventions
The University of Birmingham will use linked data from the Second-Generation Surveillance System (SGSS) data as well as data in GP records that contain SARS CoV-2 positive RT-PCR results to identify adults aged 18 years and older with confirmed COVID-19 in the Clinical Practice Research Datalink (CPRD) Aurum database (a large primary care database hosted by MHRA). Using linked Hospital Episode Statistics (HES), the research team will identify and exclude patients who have been hospitalised within 28 days of a positive SARS CoV-2 RT-PCR result or COVID-19 diagnosis.

The list of CPRD Aurum IDs of patients identified as potentially eligible (as above) by the research team will be provided to CPRD. The list of suitable patients will then be uploaded onto the CPRD Interventional Research Services Platform (IRSP). IRSP will generate a unique Global ID for each patient on that list, which will be shared with Aparito Ltd (med-tech company) to assist with verifying participants registering on the Atom5TM app. CPRD will inform participating GP practices that the patient list is available for them to review by logging onto IRSP. GPs will identify the patients using the corresponding EMIS ID and screen them for their suitability for this study.

GPs will then invite eligible patients to take part via invitation letters, text message or email which will contain the patient information sheet (PIS) and a unique one-time onboarding code for the Aparito Atom5 TM app. Patients will then log on to the Atom5 TM app and provide e-consent (which includes confirming their eligibility) and log data on their symptoms and patient-reported outcomes (PROs). Participants will be asked to complete the PROs at baseline and thereafter monthly for a period of 12 months. From this data the researchers will identify individuals with prolonged symptoms (>12 weeks) associated with COVID-19, which will form the long COVID cohort.

Matched controls
Sampling from the CPRD Aurum database, the researchers will generate a propensity score-matched control population of 500 individuals without a positive SARS CoV-2 RT-PCR result (Control Group 1) and 500 individuals with COVID-19 without Long COVID (Control Group 2), to assess the additional burden of Long COVID symptoms beyond what is observed in the infected population. CPRD will inform participating GP practices of these patients and will ask them to

check their suitability for recruitment. The list of suitable patients will then be recorded on IRSP with the generation of a unique Global ID. These patients will then be invited to participate in the study using the same process as the patients in the COVID-19 cohort and will be asked to complete the same questions.

Bio-sampling and wearables (BioWear) sub-cohort
The researchers will identify distinct symptom clusters (syndromes) using linked data from CPRD and data collected via the Atom5™ platform. A random sample of up to 300 participants (200 participants with Long COVID, with 50 sampled from each of the four most prevalent Long COVID syndromes, and 50 participants from each of the two control groups) who have previously consented to be contacted for bio-sampling will be identified and invited to take part in the BioWear sub-study.

Selected participants will be sent an invitation to participate and the BioWear sub-study PIS via the Atom5TM app, SMS message or email or by post for those who have expressed having difficulty accessing digital platforms. Those individuals showing an interest in taking part will be contacted by a member of the research team to arrange a date and time for blood and saliva sample collection and to be provided with a wearable device (Garmin Vivosmart4).

Bloods and saliva samples will be collected at a single time point (approximately four months post-study enrolment). Participants will be asked to wear the Garmin device continuously for four consecutive weeks (except when recharging the devices) when they first receive the device, at 6 months and then at 12 months. During each week of use, participants will be prompted to undertake a 40-step test, which will involve participants being asked to walk 40 steps as an exertional test to assess for changes in heart rate and oxygen saturation before and after the test.

Co-production workshops
The researchers will invite individuals who have an interest in treatments for Long COVID to take part in a series of expert consensus and co-production workshops.

Participants will be recruited from advertisements (distributed in newsletters and social media), word of mouth/known contacts (snowballing), patient support groups (including LongCOVIDSOS), research networks, and Long COVID clinics. Those expressing an interest in participating in the workshops will be given or sent the PIS electronically or by post prior to the event. In addition, the research team will explain the purpose of the research, the format of the workshop and invite participants to ask questions at the beginning of each workshop. Workshops will include presentations from the research team and group discussions. Participants will be asked their opinions about different treatments for Long COVID and how these could be adapted for remote delivery.

(added 09/04/2024)
The project culminates in a feasibility study of a decentralised trial of pacing interventions for long COVID.

Intervention Type
Mixed

Primary outcome measure
Symptoms measured using the Symptom Burden Questionnaire for Long COVID TM at baseline and monthly for 12 months

Secondary outcome measures
1. Fatigue measured using The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) at baseline and monthly for 12 months
2. Breathlessness measured using the modified MRC Dyspnoea Scale at baseline and monthly for 12 months
3. Recovery from COVID-19 measured using the COVID-19 core outcome measure for recovery at baseline and monthly for 12 months
4. Mood and mental health measured using PHQ-2, GAD-2 and PCL-2 at baseline and monthly for 12 months
5. Quality of life measured using EQ-5D at baseline and monthly for 12 months
6. Mortality assessed using linked Office for National Statistics mortality records at 12 months
7. Hospital admissions assessed using linked Hospital Episode Statistics Admitted Patient Care data at 12 months

Overall study start date
01/03/2021

Completion date
01/03/2023

Eligibility

Key inclusion criteria
Non-hospitalised individuals aged 18 years and older with a positive RT-PCR test for SARS-CoV-2 in CPRD Aurum (minimum 2000 participants)

Propensity score-matched individuals without a diagnosis of COVID-19 (suspected or confirmed) in CPRD Aurum and without a positive SARS CoV-2 RT-PCR result and without a record of hospital admission within 28 days of the index date (minimum 500 participants)

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 3040; UK Sample Size: 3040

Key exclusion criteria
Aged under 18 years or hospitalised for COVID-19:
1. Individuals without a positive SARS CoV-2 RT-PCR test result in CPRD Aurum
2. Individuals with a hospital admission within 28 days of a positive SARS CoV-2 RT-PCR result in CPRD Aurum

3. Individuals aged under 18 years
4. Individuals unable/unwilling to provide informed consent
5. Individuals unable/unwilling to undertake the protocol activities
6. Individuals deemed appropriate for exclusion by their GP (e.g., on a palliative care register)

Matched controls - Group 1 (minimum of 500 participants):
1. Individuals with a diagnosis of COVID-19 in CPRD Aurum or positive SARS CoV-2 RT-PCR result in SGSS or GP record
2. Individuals coded in their primary care record as having suspected COVID-19
3. Individuals aged under 18 years
4. Individuals unable or unwilling to provide informed consent
5. Individuals unable or unwilling to undertake the protocol activities
6. Individuals deemed appropriate for exclusion by their GP (e.g., on a palliative care register)

Matched controls - Group 2 (50 participants):
1. Participants unable/unwilling to provide informed consent
2. Participants unable/unwilling to undertake the protocol activities
3. Participants deemed appropriate for exclusion by their GP (e.g., on palliative care register)

Bio-sampling and wearables (BioWear) cohort (200 Long COVID participants, 50 participants from Control Group 1 and 50 participants from Control Group 2):
1. Participants who have not previously consented to be contacted for bio-sampling/use of wearables
2. Participants unable/unwilling to provide informed consent
3. Participants unable/unwilling to undertake the protocol activities

Co-production workshops:
1. Individuals unable/unwilling to provide informed consent
2. Individuals unable/unwilling to attend a co-production workshop

Date of first enrolment
22/11/2021

Date of final enrolment
22/05/2022

Locations

Countries of recruitment
United Kingdom

Study participating centre
NIHR CRN: West Midlands
James House
Newport Road
Albrighton
Wolverhampton
United Kingdom
WV7 3FA

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
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Birmingham
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B15 2GW

Sponsor information

Organisation
University of Birmingham

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Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

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

Results and Publications

Publication and dissemination plan
Results will be published, presented at conferences and made available for use by other researchers. The researchers will host a study-specific website and Twitter account and will share lay summaries coproduced with our patient partners.

Patient and public involvement
People with COVID lived experience have co-designed this research proposal. A lived experience advisory panel will work with the researchers throughout the project and meet regularly to contribute to all aspects of the study.

Intention to publish date
01/01/2023

Individual participant data (IPD) sharing plan
The data generated during the study will be made available to other research teams upon reasonable request to the Chief Investigators Dr Shamil Haroon and Professor Melanie Calvert (tlcstudy@contacts.bham.ac.uk).
Each of the datasets used within the project can be shared but this will require an application to

the original data controllers. The data are released to a specific research team for a specific project and so subsequent use will likely require independent approvals.
The analysis-ready locked study dataset including data from the various sources on consented study participants will only be accessed by University of Birmingham staff and may be used in future for further research. This dataset will be controlled by the University of Birmingham and any requests for access to this will be reviewed and approved by them.
Information on the individual datasets used within this project is already available from the data controllers. All CPRD datasets are listed on the HDR UK Gateway.
The researchers will also publish outputs from the project with information on available data and data access.
The research consortium for this project are users of the data under permission and so requests for sharing will need to be submitted to the original data controllers.
Requests for access to anonymised CPRD primary care and linked data used for the study will be subject to CPRD Research Data Governance (RDG) approvals. Applications for access to the analysis-ready dataset that contains CPRD data from unconsented patients for the purpose of validation or inclusion in an individual patient data (IPD) meta-analysis, should be made to the University of Birmingham in the first instance. The University of Birmingham will pass on this request to CPRD (as the data controller for this dataset) for approval of data sharing.
Repurposing of this analysis-ready dataset for any purposes other than the original study aims (or for validation and IPD meta-analysis) will be subject to a new CPRD research data governance (RDG) application and will need to comply with national data opt-out policies.
The core combined dataset on consented participants that will be deposited in the Research Data Archive (RDA) will only be accessible to University of Birmingham staff and supervised students. This dataset may be shared with other research groups outside the University upon reasonable request and with data access agreements in place for the purposes of prespecified analyses that fall within existing ethical approvals or with new ethical approvals in place. Decisions regarding data sharing will be made by the study Chief Investigators.
With regard to the consented patient study, we have requested permission from study participants on the consent form to share data with other research groups and industry partners. All data sharing will only include anonymised data.
Requests for access to source data from other data controllers like CPRD should be directed to the relevant data controllers and is subject to their data governance approvals. There are no other restrictions or delays to sharing of anonymised CPRD data. The analysis-ready dataset derived from anonymised CPRD data for the purpose of this study will only be accessible after the study has completed.
User responsibilities are determined by the original permissions to use the different datasets from the original data controllers but also in relation to their use of each of the Trusted Research Environments.
Only members of Aparito Ltd will have direct access to data from Atom5(TM). Access to data from Atom5(TM) to members of the TLC Study Group will be gained through data managers at Aparito Ltd.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	11/10/2021	10/11/2021	No	Yes
Protocol file	version 2.0	08/11/2021	10/11/2021	No	No

Protocol (preprint)		21/12/2021	24/12/2021	No	No
Interim results article	Symptoms and risk factors for long COVID	25/07/2022	01/08/2022	Yes	No
Protocol article		26/04/2022	01/08/2022	Yes	No
HRA research summary			28/06/2023	No	No