ISRCTN16650532 https://doi.org/10.1186/ISRCTN16650532

The UK interstitial lung disease long COVID-19 study

Submission date 20/09/2021	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 08/12/2021	**Overall study status** Ongoing	
Last Edited 01/05/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims

A commonly reported after effect of contracting COVID-19 is developing Post COVID Interstitial Lung Disease (PC-ILD). PC-ILD is inflammation, scarring (fibrosis), or both that can cause permanent lung damage. Inflammation may be reversible but can progress to fibrosis which may worsen over time. The number of people with ILD is not clear but could be high. Highlighting the disease history and risk factors for the development of lung fibrosis could help define better treatment options. This is a study of patients with suspected ILD following COVID-19 to determine the prevalence of ILD at 12 months following infection as well as factors that influence the recovery or worsening of the condition.

Who can participate?

Patients aged 18 to 99 years old with a proven COVID-19 infection who have continued to suffer respiratory (breathing) symptoms prompting further clinical care and a CT scan to determine their lung condition.

What does the study involve?

CT imaging and lung function testing will be performed as part of a routine investigation in the post-COVID clinic. For patients who consent to additional tests, these will be done by a member of the research team at the same clinic. Following assessment of post-COVID patients at baseline (3-6 months after infection), those with clinical and radiological features suggestive of ILD will be included in the study population. A repeat CT will be offered at 12 months (+/- 3 months) after infection. Those with no clinical, radiological or physiological features of ILD will be invited to enrol as part of the control cohort. Participants will also be offered lung function testing at 3 and 12 months and asked to complete questionnaires assessing for breathlessness, fatigue, cognition and quality of life. They will be offered the opportunity to perform a walk test to assess aerobic capacity and further blood tests for genetic testing and further analysis.

What are the possible benefits and risks of participating?

These procedures are purely for research and there will be no direct benefit to participants. However, it is to be hoped that the research will lead to an improved understanding of the causes of lung fibrosis following COVID-19 and the mechanisms by which it occurs. The researchers will collect data from the participants' records, there is minimal risk, and all

information will be used anonymously. If participants agree to provide additional samples, being a part of this study means that more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. All of the things done as part of this research are very safe and happen in the hospital on a daily basis. There is a risk of pain or discomfort when samples are taken. During the study participants will have blood samples taken. This is a standard procedure which is unlikely to cause you any problems but can sometimes cause discomfort. Collecting a blood sample from a vein may cause pain, swelling, bruising, lightheadedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick. However, all venepuncture and blood sampling will be conducted by a fully phlebotomy trained member of the clinical research team. The researchers will use the samples to try and work out what things contributes to the risk of getting COVID-19, how severe the infection is and how people recover from it. These will be looked at in batches and will not have any details on them about who they belong to, therefore, the researchers will not attempt to identify participants or inform them of any results from the sample testing. Participants and their GPs will not receive individual results from these tests as they are not being used for diagnostic purposes, they are solely for research and safety purposes.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
March 2021 to March 2027

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Prof. Gisli Jenkins, gisli.jenkins@imperial.ac.uk
2. Dr Valerie Quinn, v.quinn@imperial.ac.uk

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
297891

ClinicalTrials.gov number
NCT05514522

Secondary identifying numbers
CPMS 50234, IRAS 297891, 21IC6978

Study information

Scientific Title
The UK Interstitial Lung Disease Long-COVID19 study (UKILD-Long COVID): understanding the burden of interstitial lung disease in long COVID

Acronym
UKILD-Long COVID

Study objectives
The primary objective of the study is to determine the prevalence of interstitial lung disease (ILD) at 12 months following SARS-CoV-2 infection and whether clinical severity correlates with the severity of ILD in survivors.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 18/08/2021, London Riverside (Health Research Authority, Temple Quay House, 2 The Square, Temple Quay, Bristol, BS1 6PN, UK; +44 (0)207 104 8184; christian.bertholle@hra.nhs.uk, riverside.rec@hra.nhs.uk), REC ref: 21/HRA/3313

Study design
Observational; Design type: Clinical Laboratory Study

Primary study design
Observational

Secondary study design
Clinical laboratory study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
See additional files

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

Interventions
Participants will be required to attend up to three clinic visits over a 12-month period: at three months post initial COVID infection, 6 months and 12 months.

Recruitment
1. Participants who have been recruited to the national PHOSP-COVID study have all consented for their data to be used. Similarly, participants of other studies or trials that recruit SARS-CoV-2 infected patients will also be approached.
2. COVID-19 patients attending post-COVID clinics will be identified, and eligibility assessed by review of medical records by the clinical team. They will be provided with an invitation letter and study information. If interested they will be approached by the PC-ILD study team who will supply study information in person or by post or email. Potential participants may be re-contacted on the day of, or up to seven days following, initial contact to discuss any queries they may have and assess eligibility.

Screening and Eligibility Assessment
Patients will be assessed by the clinical teams for eligibility against the inclusion or exclusion criteria. If they satisfy the inclusion and exclusion criteria of the protocol, they will be invited to participate. Pre-screening for eligibility will take place prior to consent. It will be done by the direct care team using patient notes. There will be no access to patient identifiable data outside of the direct care team prior to consent.

Visit 1
This will be at about 3 months post initial infection. The research team will re-review eligibility and obtain written informed consent. They will take a clinical history, perform a brief

examination, measure height and weight and calculate body mass index (BMI). Blood samples will be taken, lung function tests performed, and participants will be asked if they would like to undergo a walk test to assess fitness and symptoms of breathlessness. They will be taken through a series of questionnaires assessing quality of life, frailty, personal health, cognition, breathlessness and fatigue.

Visit 2 & 3
An optional visit 2 will be at around 6 months after infection and visit 3 will be around 12 months. The assessments described for visit 1 will be repeated.

Other investigations
Participant consent will be sought to obtain hospital electronic patient records for clinical outcome data and images from the time of infection, hospitalisation and follow up.

Controls
Individuals who meet the criteria for initial study inclusion (COVID-19 and clinical indication for CT scanning) but have no clinical, radiological or physiological features of ILD will be invited to enrol as part of the control cohort for follow up.

Sample size justification
This study will recruit 2,000 patients from post-COVID clinics and will run alongside the PHOSP-COVID study which will recruit up to 10,000 participants. Post-COVID related breathlessness has been reported to affect approximately 40% of people hospitalised with severe disease and 10-20% of people who suffered mild COVID-19. Preliminary analysis from UK and international studies have described up to 80% of hospitalised COVID-19 patients have the presence of symptoms, radiology and lung function changes concordant with ILD, depending on the severity of the underlying illness. It is anticipated that approximately 20% (2400/12000) of people recruited into the UKILD-Post COVID study will have features consistent with ILD for characterisation, which will provide a sufficient sample size for descriptive analysis, evaluation of incidence and prevalence, and assessment of risk factors.

Planned Interim Analyses
A planned interim will be performed after the 3-month follow up of the first 100 participants to provide initial insights into expected radiological patterns and to preliminarily describe the potential PC-ILD burden for the support of clinical management. A second planned interim will be performed at 6 months to inform recruitment to study.

Patient and Public Involvement
Action for Pulmonary Fibrosis charity and patient partners have been involved from the conception of this study to inform study design and conduct. They will also form part of the ongoing steering committee appraising patient-facing material and facilitating the dissemination of findings to IPF patients and their families.

Intervention Type
Other

Primary outcome measure
Multi-disciplinary team (MDT) confirmed diagnosis of ILD at 12 months (+/- 3 months) after acute infection

Secondary outcome measures

1. Lung function decline ≥10% OR worsening extent of ILD on CT scan using image analysis or MDT discussion at 3 and 12 months (+/- 3 months) after acute infection
2. Resolution of ILD: any of the following: ≥10% relative improvement in FVC, DLco, or reduction of radiological extent at 12 months (+/- 3 months) post SARS-CoV-2
3. Persistence of ILD in those not meeting the definition of progression or resolution at 12 months (+/- 3 months) post SARS-CoV-2
4. Persistence of ILAs measured using Computerised Tomography at 12 months (+/- 3 months) post SARS-CoV-2
5. Markers of severity of acute infection (e.g. CRP) measured using initial clinical assessment at 12 months (+/- 3 months) post SARS-CoV-2
6. Medical therapy used for acute infection measured using clinical records at 12 months (+/- 3 months) post SARS-CoV-2
7. Breathlessness measured using the Medical Research Council dyspnoea scale, Dyspnoea 12 at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
8. Fatigue measured using FACIT-F at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
9. Cognition measured using the Montreal Cognition Assessment (MOCA) at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
10. Quality of life measured using Short Form-36 (SF-36), EQ5D-5L at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
11. Impact of COVID19 on aerobic capacity and endurance measured using the incremental shuttle walk test or cardiopulmonary exercise test, if clinically indicated, at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection

Exploratory:
1. Exploratory circulating biomarkers measured using whole blood RNA sequencing (including peripheral blood mononuclear cells) and analysis of epigenetic modifications and proteomics at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
2. Serological and cellular measures of epithelial and endothelial injury and thrombosis measured using serum biomarkers of epithelial and endothelial injury, NETosis and thrombosis, cellular measurements, and serum/plasma Nordic biomarkers, LRG-1, MMP-7 etc; NETs at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection
3. Genetic risk factors for lung fibrosis and radiological progression, continuously and dichotomised, assessed using genome-wide array genotyping, genetic testing from blood/saliva of putative candidate genes, and use of genomic data and telomere length in a subset at no sooner than the 3-month visit
4. Laboratory parameters (including CRP, FBC) and extent of ILD in patients measured using blood and serum analysis at 3 months, 6 months (+/- 6 weeks) and 12 months (+/- 3 months) post SARS-CoV-2 infection

Overall study start date
12/03/2021

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Aged 18 to 99 years old
2. Evidence of SARS-CoV-2 infection confirmed by PCR or serology 3 months (+/- 6 weeks) earlier

3. Clinical indication for a chest CT scan as per clinician judgment
4. Participants who have been identified and consented for the main PHOS-PCOVID study are also eligible to join this study
5. Allow inclusion of patients who are receiving up to 10 mg of prednisolone a day

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 2000; UK Sample Size: 2000

Total final enrolment
183

Key exclusion criteria
1. Life-limiting illness within 12 months
2. Significant pre-existing lung disease prior to March 2020, which in the investigator's judgement could make the chest CT scans difficult to interpret

Date of first enrolment
18/08/2021

Date of final enrolment
24/02/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre
University College London Hospital
250 Euston Road
London
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NW1 2PG

Study participating centre

Royal Brompton Hospital
Sydney Street
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Study participating centre
John Radcliffe Hospital
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Sponsor type
University/education

Website
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ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
Medical Research Council; Grant Codes: MR/W006111/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The final results of the study will be disseminated in the form of a manuscript/s in a peer-reviewed scientific journal, presented at national and international conferences and in local meetings. In addition, where relevant, data from potential interim analyses will be presented at (a) relevant congress (es). In addition, the study database will be made available for future research.

Intention to publish date
31/08/2023

Individual participant data (IPD) sharing plan
The PHOSP COVID study (ISRCTN10980107) is a national consortium that provides a platform to study the long-term consequences of COVID19 hospitalisations. The study described here will aim to recruit a further 2000 individuals with proven COVID-19 who were not hospitalised but presented to Long-COVID clinics with persistent respiratory symptoms such as breathlessness or cough and are referred for cross-sectional imaging (computer tomography, CT) at baseline (3 months weeks after their first COVID-19 symptoms). Data from both studies will be collated and stored in a REDCAP study database available for future research. Data will be shared within a TRE at Edinburgh university. Currently both studies are continuing to build and amass data so the data is not wholly available for other research. Once the database is completed, details and availability will be clarified.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.0	18/05/2021	02/11/2021	No	Yes
Protocol article		01/09/2021	02/11/2021	Yes	No
Protocol file	version 1.2	28/08/2021	02/11/2021	No	No
HRA research summary			28/06/2023	No	No