STUDY PROTOCOL

FOcused **L**ongitudina**L** **O**bservational study to improve kno**W**ledge of COVID-19 (FOLLOW-COVID)

Study Acronym	FOLLOW-COVID
Lay title	**FO**cused **L**ongitudina**L** **O**bservational study to improve kno**W**ledge of COVID-19
Sponsor	University of Dundee
Sponsor Ref number R&D Number	3.013.20 2020ID40
Funder	Chief Scientist Office, Scottish Government British Lung Foundation
Chief Investigator	Dr David Connell
REC Number	20/YH/0265
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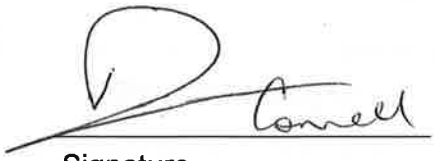
PROTOCOL APPROVAL

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Dr David Connell		25/09/20
Chief Investigator	Signature	Date

	Mike Lonergan	25/09/2020
Individual Responsible for Statistical Review	Signature	Date

Protocol Development

Chief Investigator, Dr David Connell: Initial draft, review and final approval

Co-Investigator, Prof. James Chalmers: Review

Co-investigator, Dr Amelia Shoemark: Review

Co-Investigator, Dr Benjamin Parcell: Review

Co-Investigator, Dr Alison Dicker: Review

Co-Investigator, Dr Manish Patel: Review

Co-Investigator, Dr Devesh Dhasmana: Review

Co-Investigator, Dr Beth Sage: Review

Co-Investigator, Dr Gourab Choudhury: Review

Co-investigator, Prof. Chim Lang: Review

Co-investigator, Prof. Faisel Khan: Review

Co-investigator, Prof. Graham Leese: Review

Co-investigator, Dr Samira Bell: Review

Study Manager, Stephanie Gallant: Review

Senior Research Statistician, Dr Mike Lonergan: Review

STUDY SUMMARY/SYNOPSIS

Study Title	**FO**cused **L**ongitudina**L O**bservational study to improve kno**W**ledge of COVID-19
Study Design	Prospective observational cohort
Study Population	Individuals previously diagnosed with COVID-19 disease, including a subset with severe ARDS
Sample Size	300
Planned study period	6 years
Clinical phase duration	6 months
Follow up phase duration	Up to 25 years

Primary	Objectives To describe the consequences of COVID-19, on the airway epithelial microbiome, and on longitudinal lung epithelial and vascular function, in a cohort of patients who have had a spectrum of disease as a result of infection with SARS-CoV2.	Outcome Measures From 3-6 months post-COVID-19, describe the early longitudinal changes in the airway epithelial microbiome and mycobiome A detailed description of the early (3-6 months) regenerating ultrastructural changes in the nasal airway epithelium, using a combination of video microscopy, electron microscopy, and cell culture techniques, in a spectrum of patients recovering from COVID-19. Using non-invasive techniques, perform assessments of microvascular and macrovascular endothelial function, arterial stiffness, and vascular inflammation, in the 3-6 months following severe and non-severe COVID-19; these can be linked to inflammatory intravascular gene expression in PBMCs and whole blood.

Secondary	Objectives Describe neutrophil function in survivors of severe COVID-19 pneumonia. To generate a biobank of samples from patients who are recovering from COVID-19, which can later be used to identify and predict recovery from severe COVID-19 across a range of health domains, including diabetes. To determine long term healthcare resource utilisation in patients who have had COVID-19 disease.	Outcome Measures To characterise neutrophil function in survivors of severe COVID-19 pneumonia, including those who had ARDS, and link to clinical phenotypes. To characterise the effect of COVID-19 on complications and management of diabetes, using the SCI-diabetes database and look for the underlying associated biomarkers relating to metabolic function (such as adipokines) that might be associated with differential outcomes. Long-term assessment of healthcare utilisation using electronically linked health care records, and phone interviews, and linking these outcomes with the work streams described above, and with biomarker discovery from stored samples.
Inclusion Criteria:	Previous clinical (only if hospitalised) or microbiological (if hospitalised or non-hospitalised) diagnosis of COVID-19 disease. Age $\geq$18 years (no upper age limit)	
Exclusion criteria:	Unable to give informed consent. Participation is not in the interests of the patient as determined by the investigator (e.g. palliative care).	

	If an individual has any symptoms compatible with current COVID-19 (as per the Health Protection Scotland Guidelines relevant at that time). If an individual is currently isolated following a contact with COVID-19. If an individual has had an upper respiratory tract infection in the preceding 14 days. Nasal brushings only: Patient has a history of significant epistaxis or is anti-coagulated.

1 BACKGROUND AND RATIONALE

Coronaviruses (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV).

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-COV-2 and the disease caused by this virus has been designated COVID-19. The disease has now spread to affect millions of patients worldwide with widespread community transmission across the globe.

Mortality from COVID-19 has been estimated at 0.66% of infected patients[1] and occurs most frequently because of the development of Acute Respiratory Distress Syndrome (ARDS). In the UK, one third of patients admitted to hospital with COVID-19 have died, and in intensive care, survival is approximately 50%, significantly worse than other viral pneumonias[2]. In addition to ARDS, the use of renal replacement therapy in ICU is also associated with poor outcome, and general risk factors for death include Age, Male Sex, Obesity, Chronic Lung Disease, Cardiovascular Disease and Diabetes[3]. It is notable that risk factors that influence vascular endothelial health, such as diabetes and cardiovascular disease, have exerted a significant effect on outcome.

ARDS occurs in up to 10% of all COVID-19 cases[3], while extensive pulmonary infiltrates have also been reported in patients not requiring mechanical ventilation. The pulmonary effects of SARS-CoV-2 are thought to be mediated through a combination of interstitial damage and endothelial inflammation, leading to a combination of both ventilation and perfusion defects[4]; this seems to be in contrast to changes seen in severe influenza where endothelial disease is less common[5]. Influx of neutrophils to the lung, leading to damage from host-derived proteases, is a key part in this pathogenic process.

While most patients with COVID-19 are likely to make a full recovery, previous studies in other severe coronavirus diseases such as SARS suggest that a proportion of patients, perhaps as high as 4%, will experience long term irreversible pulmonary disease[6]. Persistent respiratory symptoms and poor quality of life are also described and have already been seen in UK cohorts at an early stage (own unpublished data). Given the concerns around post-COVID-19 lung damage, longitudinal changes in lung inflammatory processes (such as those driven by or ameliorated by neutrophils) and the pulmonary microbiome post-COVID-19 may be important in shaping the outcomes of patients with structural lung disease.

The multi-site PHOSP-COVID Study (in which D Connell and J Chalmers are also Principal Investigators) will study these broad changes at scale within the UK; yet the granular detail of how these outcomes are reflected in structural and microbiological changes in the airway and in the lung also need to be examined, so that the biology of the post-COVID-19 lung can be better understood. Studying regenerative epithelial changes in the airway following COVID-19 disease, along with longitudinal changes in the airway epithelial microbiome and neutrophil function following illness, are the planned key **pulmonary/airway** work streams in FOLLOW-COVID and complement the work of PHOSP-COVID.

Given the ubiquity of the receptor for SARS-CoV2 (ACE2), the virus has the ability to affect multiple organ systems. Enhanced ketosis in patients with diabetes, strokes, myocardial infarctions, as well as gastrointestinal ischaemia have all been described as occurring following COVID-19[7]. There are also reports of a range of vascular dermatological complications including Raynaud's phenomenon. Consequentially, long term effects on other aspects of non-pulmonary health, particularly in endothelial function, cardiovascular disease, and diabetes, have also been hypothesised to follow severe COVID-19 and may compound the effects on the lung. Understanding these broader and more nuanced effects will be important given their wide-reaching effects on the nation's future health. This is particularly the case given that established risk factors noted above, such as obesity or diabetes, which make severe disease with COVID-19 more likely, may also later influence longer term cardiovascular outcome. Work in the linked areas of vascular function, metabolism and diabetes, are therefore the key **non-pulmonary** work streams in FOLLOW-COVID.

By May 2020, over 18,000 Scottish people have been found to have been infected with SARS-Cov-2, with over 2,450 deaths. Many hundreds of patients have already been treated in Intensive Care, with over 4,000 treated in hospital for COVID-19 pneumonia[8]. The long-term effects on these individuals is presumed to be significant, and future waves of disease may increase these numbers greatly. The impact on Scottish healthcare utilisation in the future may be very significant as a result. One example is that of Chronic Kidney Disease: it is not yet known how the impact of severe COVID-19 - where Acute Kidney Injury and the requirement for Renal Replacement Therapy conferred a significantly higher risk of death - will impact on future risk of CKD and if this can be predicted from early biomarker analysis.

To start to understand these challenges, this study will recruit a cohort of individuals affected by COVID-19 so that they can be studied over time in a focused and detailed series of pre-defined pulmonary and non-pulmonary workstreams centred around epithelial and endothelial health. These patients may also be part of the multi-site UK PHOSP-COVID study, which aims to provide a more broad-reaching overview of the short, medium, and long-term effects of hospitalisations with COVID-19, particularly around lung disease on its broadest terms. Initially, data collection will occur over 6 months in order to provide urgent focused data to help inform Scottish clinical practice with regard to post-COVID-19 health, but the cohort will be established so that the patients can be followed-up for up to 25 years, and linkage to longer term health outcomes can be explored.

2 STUDY OBJECTIVE AND OUTCOMES

Primary objectives:

- To describe the consequences of COVID-19, on the airway epithelial microbiome, and on longitudinal lung epithelial and vascular function, in a cohort of patients who have had a spectrum of disease as a result of infection with SARS-CoV2.

Secondary objectives:

- To describe neutrophil function in survivors of severe COVID-19 pneumonia.
- To generate a biobank of samples from patients who are recovering from COVID-19, which can later be used to identify and predict recovery from severe COVID-19 across a range of health domains, including diabetes.
- To determine long term healthcare resource utilisation in patients who have had COVID-19 disease.

Clinical outcomes, against which it will be possible to track changes over time, and test biomarkers, will include:

-Mortality

-Healthcare utilisation in broad terms, including that for diabetes, renal disease, cardiovascular disease and pulmonary disease.

-Symptom burden and Quality of Life

-Frequency and type of Pulmonary Infections

2.1 Objectives

The broad study objectives are to recruit and study over time a cohort of patients who have had COVID-19, particularly severe disease; understand the effect this has had on their epithelial and vascular function; and how these effects are associated with later healthcare-related clinical outcomes such as pulmonary infections, diabetic management and cardiovascular disease. Specifically:

-To characterise the microbiome of the airway epithelial surface in patients following COVID-19 lung disease within 6 months of recovery from acute illness.

-To investigate the ultrastructural and functional consequences to the airway epithelium following COVID-19 lung disease within 6 months of recovery from acute illness.

-To characterise vascular function in patients who have had severe and non-severe COVID-19 disease, stratified by presence of pre-morbid cardiovascular disease and diabetes.

-To characterise neutrophil function in survivors of severe COVID-19 pneumonia, including those who had ARDS.

-To characterise the effect of COVID-19 on complications and management of diabetes, using the SCI-diabetes database and look for the underlying associated biomarkers relating to metabolic function (such as adipokines, inflammatory markers, and hormones associated with fat metabolism) that might be associated with differential outcomes.

-To generate a biobank of samples that will allow the future testing of biomarker-led hypotheses in the prediction of healthcare utilisation and prediction of recovery from COVID-19.

2.2 Outcomes

Aim: From 3-6 months post-COVID-19, describe the early longitudinal changes in the airway epithelial microbiome and mycobiome (work here complements the microbiome components of PHOSP-COVID, which will look at sputum samples).

Aim: A detailed description of the early (3-6 months) regenerating ultrastructural changes in the nasal airway epithelium, using a combination of video microscopy, electron microscopy, and cell culture techniques, in a spectrum of patients recovering from COVID-19.

Aim: Using non-invasive techniques, perform assessments of microvascular and macrovascular endothelial function, arterial stiffness, vascular inflammation, and fat metabolites in the 3-6 months following severe and non-severe COVID-19; these can be linked to inflammatory intravascular gene expression in PBMCs and whole blood.

Aim: From 3-6 months post-COVID-19, describe neutrophil function in patients recovering from severe COVID-19 pneumonia, including those with ARDS.

Aim: Linking with the SCI-Diabetes database to obtain a comprehensive analysis of the impact of COVID-19 on diabetes care in affected patients and linking this to changes in serum metabolic biomarkers obtained 3-6 months following COVID-19.

Aim: Long-term assessment initially over 5 years and up to 25 years of healthcare utilisation using electronically linked health care records, and phone interviews, and linking these outcomes with the work streams described above, and with biomarker discovery from stored samples.

3 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

3.1 Study description

This is a prospective observational study in hospitals in Scotland. Patients who have had a diagnosis of COVID-19, including those not hospitalised, will be recruited to this study following informed consent. Potential participants will be approached by a member of the treating medical team who will discuss the study with them and provide a copy of the PIS to consider. If hospitalised, this will be done towards the end of their hospital admission, or up to 6 months following discharge from hospital. Non-hospitalised patients will be approached in outpatient COVID-19 convalescence clinics, or via local virological databases. Study invitation may be by letter. Basic demographic data and medical history will be assessed from the patient and the case notes, contemporaneously and in retrospect where necessary. Details of the patient's care (including care in high dependency or intensive care) during their

acute illness and convalescence with COVID-19 will be recorded. If a hospitalised patient, they may be simultaneously recruited into another UK-based follow-up study (PHOSP-COVID) which will study a wide variety of outcomes including those relating to quality of life and lung health.

Approximately 3-6 months following discharge, or from episode of illness if not an inpatient, the patient will provide blood samples, a urine sample, and a nasal and throat swab taken for the planned microbiome studies. Patients from the NHS Tayside study site will have a nasal epithelial brush for the planned epithelial airway studies. If able, they will be asked to fast for 10 hours prior to the blood tests so that fasting blood ketones can be measured. The airway brush and swab samples will all be processed as per standardised laboratory protocols for the studies into nasal epithelial function and the airway microbiome respectively. The blood and urine samples will be processed as per laboratory protocols, with samples stored as a biobank for the endothelial and diabetes studies, as well as for future studies into healthcare utilisation.

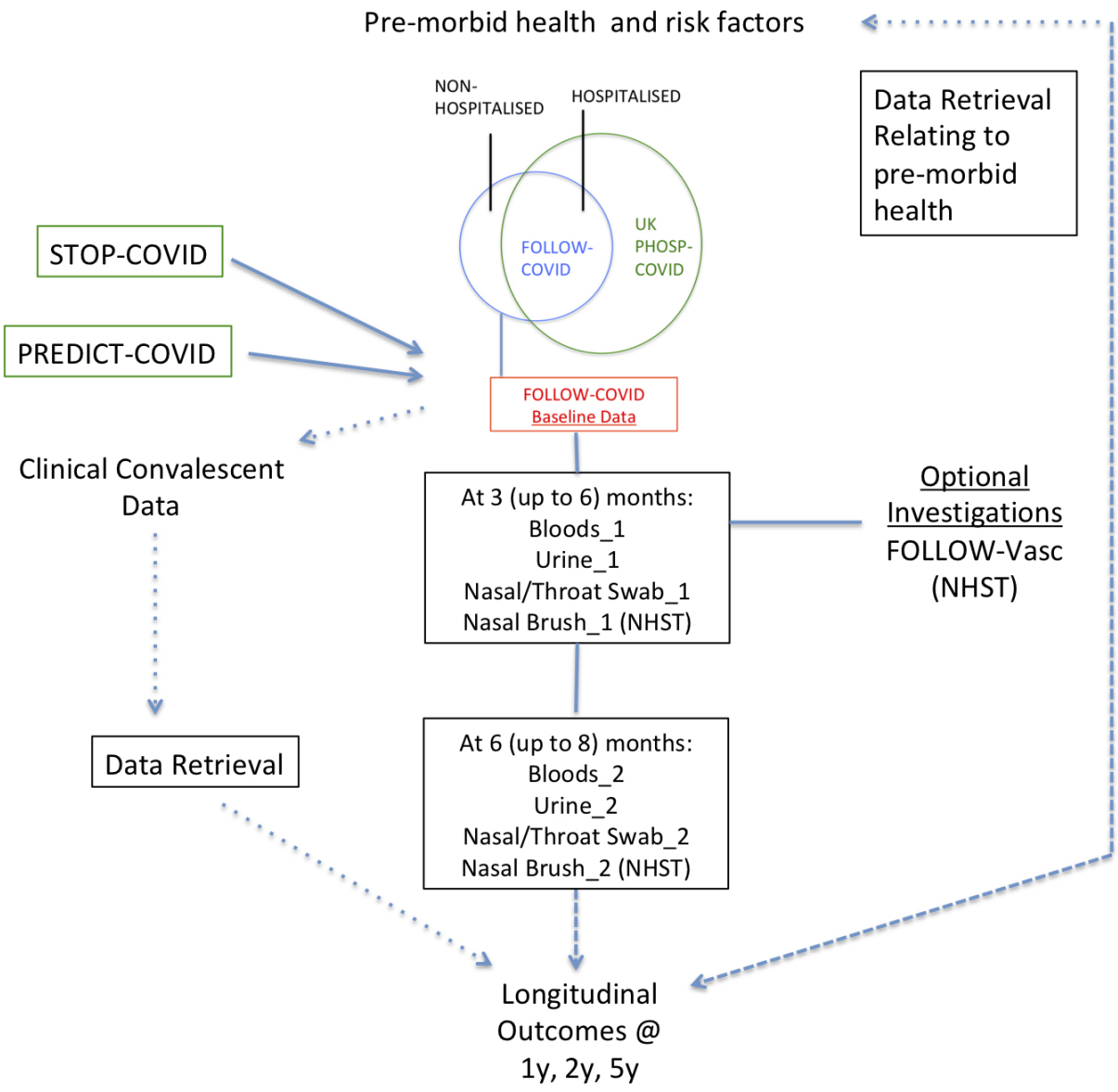
At approximately 6-8 months, they will be invited to repeat the blood samples, urine sample, nasal brush and airway swab samples.

Between 3 and 6 months, patients from NHS Tayside - approximately 120 - will be invited to take part in detailed, non-invasive tests relating to vascular function (designated as FOLLOW-VASC within this study). Microvascular endothelial function will be assessed using iontophoresis of vasoactive chemicals and laser Doppler imaging. Assessment of macrovascular function will be performed by measuring flow-mediated dilation (FMD) of the brachial artery using an 8-15 MHz linear array ultrasound. Finally, systemic arterial stiffness will be measured using aortic pulse wave velocity and augmentation index.

There will be phone call assessments at 1 year, 2 years and 5 years following discharge from hospital. Electronic medical record linkage will be used to look at contacts with primary care and comprehensive healthcare resource utilisation during the follow-up period from 6 months onwards up to 25 years; the SCI-diabetes database will be used to extract data specifically for patients with diabetes, to assess the effect of COVID-19 on longer term diabetes control, body weight and complications within the cohort (designated FOLLOW-DIABETES within this study).

Reasonable travel expenses will be available to participants to attend study visits.

3.2 Study flowchart



3.3 Study Assessments

	Time after discharge/episode of illness			
	Study entry	3 (to 6) months	6-8 months	1, 2 & 5 years
Informed consent	X			
Baseline information	X			
Blood		X	X	
Urine		X	X	
Nasal and Throat Swab		X	X	
Nasal brushing (NHS Tayside patients)		X	X	
Endothelial/Vascular Optional Investigations FOLLOW-VASC (NHS Tayside patients)		X		
Phone call assessment				X
Long term follow-up via records inc. FOLLOW-DIABETES work using SCI-Diabetes			X	X (up to 25 years)

Up to 50ml of blood will be taken at each indicated venepuncture assessment (as other studies are being conducted to which the patient may also be recruited, no more than 100ml of blood between all studies will be taken at any time point). This will be split for isolation of peripheral blood mononuclear cells (PBMCs), neutrophils, and plasma (if at NHS Tayside study site); and also serum (all study sites). At all study sites, a blood tube for gene expression analysis will also be taken and an EDTA tube for genetic analysis. Some routine blood tests for Full

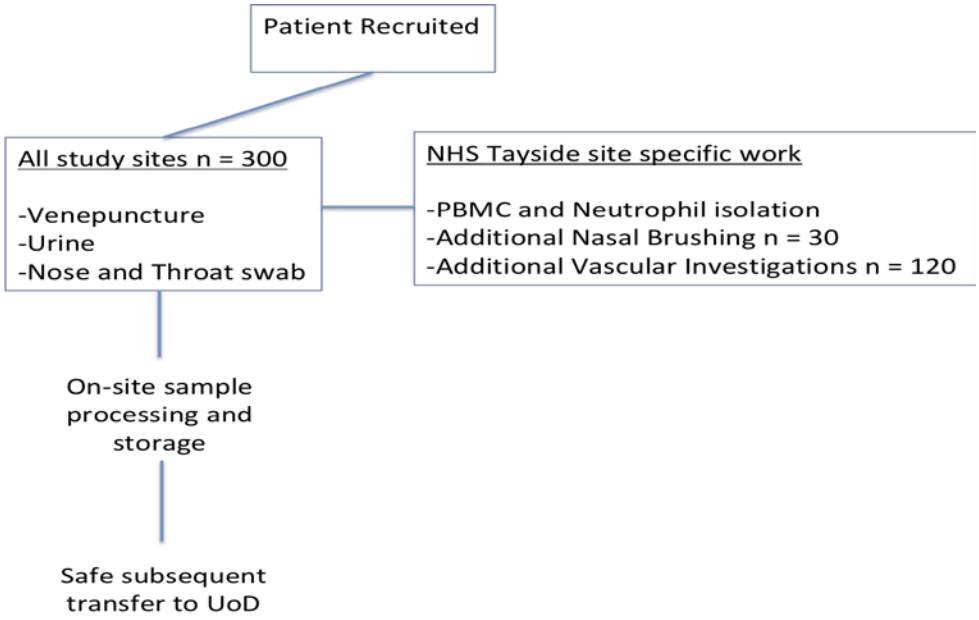
Blood Count, and Urea and Electrolytes and measurement of HbA1c and serum lipids (if appropriate) will also be taken (unless already taken for clinical purposes).

Where indicated, a urine sample will be taken and dipsticked, and tested for protein content. The remainder will be stored for further analysis and sent for albumin creatinine ratio (ACR) where relevant (e.g. patients with diabetes).

A nasal and throat swab will be taken at all study sites, using an approved standard operating procedure, and safely stored at the study site until used for the sequencing/microbiome studies.

A nasal brushing will be taken from 30 patients at the NHS Tayside study site using an approved standard operating procedure. This involves removing surface cells from the mucosal lining of the nose with a small cytology brush. This will be processed using standardised laboratory protocols for cell culture and microscopy.

For patients who have the vascular/endothelial optional investigations (approximately 120 patients from NHS Tayside study site), measurements of microvascular function will be conducted by measuring skin vascular responses to iontophoresis of 1% acetylcholine (endothelium-dependent) and sodium nitroprusside (endothelium-independent). Skin perfusion will be measured using a laser perfusion system (moorLDI, Moor Instruments, Axminster, UK). Assessment of macrovascular function will be performed by measuring flow-mediated dilation (FMD) of the brachial artery using an 8-15 MHz linear array ultrasound according to standardised guidelines. In addition, the endothelium-independent vasodilator response will be assessed by measuring the percentage change in brachial artery diameter following administration of 0.4mg sublingual glyceryl trinitrate (GTN). Systemic arterial stiffness will be measured using aortic pulse wave velocity and augmentation index. The waveforms of the artery from the volunteer will be recorded at the wrist (radial artery), neck (carotid artery) and groin (femoral artery) with a micromanometer using the SphygmoCor PWV and PWA system. Augmentation index, heart rate and carotid-to-femoral pulse wave velocity will be calculated.



3.4 Study safety for staff and participants

At all times the NHS policies on infection control will be closely followed to ensure the safety of both staff and participants, including the use of PPE where appropriate. We will ensure that work is undertaken in line with local and national (Health Protection Scotland) infection control protocols.

All procedures will be performed by trained staff experienced in the techniques required and discomfort will be minimised. Nasal brushings will follow relevant guidelines for safety around aerosol generating procedures.

Any incidental findings of significance to the health and wellbeing of participants will be reported to the treating medical team, the patient and their GP.

3.5 Tissue

Samples of blood, urine, and nasal and throat swabs will be taken in all study recruits. These will be processed on site, safely stored in the Clinical Research Facility, and later sent to the University of Dundee respiratory research lab for analysis. A nasal brushing will be collected in individuals from the NHS Tayside study site. Any surplus tissue will be retained for future ethically approved research for up to 10 years. Samples will be stored in the University of Dundee respiratory research lab and registered with the Tayside Biorepository.

4 STUDY SETTING

This is a multi-centre study with recruitment taking place in up to 10 hospitals in Scotland.

5 STUDY POPULATION

5.1 Eligibility Criteria

5.1.1 Inclusion criteria

- Previous clinical (only if hospitalised) or microbiological (if hospitalised or non-hospitalised) diagnosis of COVID-19 disease.
- Age ≥18 years (no upper age limit).

5.1.2 Exclusion criteria

- Unable to give informed consent.
- Participation is not in the interests of the patient as determined by the investigator (e.g. palliative care).
- Symptoms compatible with current COVID-19 (as per the Health Protection Scotland Guidelines relevant at that time).
- Currently isolated following a contact with COVID-19.
- Individual has had an upper respiratory tract infection in the preceding 14 days.
- Nasal brushings only: Patient has a history of significant epistaxis or is anti-coagulated.

5.2 Sampling

5.2.1 Size of sample

- 300 - including a proportion of patients admitted to the High Dependency Unit (HDU) and Intensive Care Unit (ICU).

5.2.2 Sampling technique

Previous COVID-19 patients will be identified while inpatients before discharge or through previous hospital records, including from virological records, 2-6 months from recovery. Patients can be approached and invited to participate in the study as inpatients, while attending a hospital clinic or by invitation letter. Letters sent will include a patient information leaflet, ICF and contact details for research staff. Those interested can contact the study team for more information. If no reply is received to the initial letter, one follow-up will take place by letter or phone call.

5.3 Recruitment

Identification of potentially eligible participants will be by a member of the medical staff or study team delegated this role by the PI. Research nurses will work closely with the managing

clinical teams who may also provide patient lists. As noted elsewhere, patients may be approached as inpatients, in COVID-19 convalescent clinics, or via telephone or preferably by letter. A PIS and invitation letter will be sent, where possible with a clinic appointment letter, and patients asked to opt-in to the research by contacting the research team.

If patients are currently in hospital, medical or research staff will return after 24 hours to ask if they would like to take part. If patients are at home, staff will ask to recontact them or arrange for them to phone the research nurses.

5.3.1 Sample identification

Research samples will be pseudoanonymised with a unique study identifier.

5.3.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. Only study staff experienced in consenting participants will be delegated this role.

Patients will be given a minimum of 24 hours to decide whether to participate and the opportunity to have any questions they have answered.

The original Informed Consent Form (ICF) will be signed by the participant and staff receiving the consent in person, by telephone or by post. The original ICF will be kept in the site file, a copy will be placed in their medical notes and a copy given to the patient.

The patients GP will be informed by letter of their participation in the study along with any relevant investigation results.

Participants will be informed that the study researchers may contact them regarding other studies may be appropriate for them. They will be able to choose whether, or not, to take part in this future research.

5.3.3 Ineligible and non-recruited participants

The reason(s) for ineligibility will be explained to the participants and any questions they have will be answered.

5.3.4 Withdrawal procedures

Participants will be informed they can withdraw at any time with no effect to their future health care. Research team contact details are provided in the PIS. Patients may miss sampling

periods without withdrawing from the study. If a patient wishes to withdraw, they can request any remaining samples be destroyed when they contact the study team.

6 DATA COLLECTION & MANAGEMENT

6.1 Data collection

Paper records (e.g. CRFs, consent forms) will be kept at the recruiting sites in a secure physical location.

Clinical data collected at visits will be recorded in a paper CRF and transferred to a password protected Excel file for ease of analysis. Associated relevant data e.g. demographics, symptoms, will also be stored electronically in Excel format. This will be pseudoanonymised and stored only with associated study identifier. No personal identifiers will be kept with medical data.

Paper CRFs will be stored in a locked filing cabinet in the clinical research facility.

CRFs will be managed in accordance with Sponsor SOP.

Data will be collected form the patient, medical notes, MDT notes, hospital clinical systems such as ICE, Clinical Portal and Ekora.

We will collect data that will include but is not limited to:

COVID Research Studies already entered

- Which studies and which meds given

Basic Individual Data

- Age
- Sex
- BMI
- Ethnicity
- Past Medical History
- Medications
- Inpatient or Outpatient
- Postcode for SIMD
- Employed/Not employed

Basic Data from Acute Admission/Readmissions

- Observations at presentation if inpatient

- Urine Dipstick if done
- Length of stay and if re-admitted
- Needed oxygen or not and how much at peak
- HDU or ICU and length of time on each
- CPAP vs HFNC vs both
- Time invasively ventilated in ICU
- Requirement for Acute/New Renal Replacement Therapy
- Other events during admissions/re-admissions: heart attack/stroke/PE etc.

Follow-up/Convalescence Data

- Symptom Questionnaires
- Clinical details of follow-up symptoms and outcomes
- Observations including ECG, urine dipstick

Blood tests/Other investigations

- Baseline, Peak, Convalescence blood tests during admission and in follow-up
- Echo if done
- CXRs at baseline and in convalescence
- Other imaging during acute illness and convalescence

SCI – Diabetes

Collects data from primary and secondary care on more than 99% of patients in Scotland with diabetes. SCI-Diabetes provides a fully integrated shared electronic patient record to support treatment of NHS Scotland patients with Diabetes. It is developed, maintained and supported by the SCI-DC Development Team, Tayside. It includes data on:

- Weight/BMI
- Blood Pressure
- Smoking, exercise & alcohol history
- Biochemistry - HbA1c, creatinine, eGRF, lipids, urine albumin,
- All prescribing
- Retinal screening outcomes
- Foot screening outcomes
- Foot ulcer data

Data extraction from electronic medical records will be completed by the Health Informatics Centre, or equivalent, and by SCI Diabetes in accordance with SOPs and GDPR.

6.2 Data management system

Data management will be conducted in accordance with Sponsor SOP.

The data management system (DMS) will be Excel.

The DMS will be based on the protocol for the study and individual requirements of the investigators. The DMS will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant.

The data will be managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate DMS completion but is responsible for completeness, plausibility and consistency of the DMS. Any queries will be resolved by the CI or delegated member of the study team.

7 STATISTICS AND DATA ANALYSIS

7.1 Sample size calculation

As the prevalence of post-COVID-19 disease is unknown it is not possible to perform an informed power calculation based on the primary or secondary endpoints. We have therefore chosen a sample size that is judged to give a representative sample of post-COVID-19 patients in Scotland. A review of the first 150 patients will be used to inform sample size re-estimations (if required) for the primary and secondary endpoints and will also utilise data arising from the UK-wide PHOSP-COVID project where appropriate.

7.2 Proposed analyses

These reflect the defined primary and secondary objectives and will include:

- Functional studies and microscopy on recovered nasal epithelial cells.
- Studies on the airway microbiome and mycobiome from nasal and throat swabs.
- Studies on blood neutrophil function.
- Studies relating to vascular/endothelial function as outlined above.

- Measurement of biomarkers related to vascular and metabolic function (yet to be defined) on urine, serum, and plasma using multiplex assays and specific assays where needed.
- Analysis of symptoms from questionnaires taken in routine clinical practice, and how these change over time, relate to burden of initial disease, and outcomes derived from analysis of electronic health records and analysis of biomarkers.
- Functional studies on PBMCs may be performed.
- Transcriptomics on peripheral blood may be performed.
- Genetic analyses from stored blood may be performed.

The methods to be used for these will be outlined in laboratory SOPs and a laboratory manual.

7.3 Missing Data

Missing data and samples are expected as part of the real life nature of sample and data collection and we will not use imputation.

7.4 Transfer of data

Patient data will be transferred between sites in accordance with the data transfer agreement.

Samples including stored tissue may be shared with commercial and non-commercial partners for research studies.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 Study management group

The study will be coordinated by a Study Management Group (SMG), consisting of the grant holder Chief Investigator (CI), co-investigators, study manager, study statistician and a representative from the British Lung Foundation.

8.2 Study steering committee

Is the same as the study management group above.

8.3 Data monitoring committee

The function of a DMC will be a combined role for the study management group.

8.4 Inspection of records

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 Ethical conduct of the study

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate NHS REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 Public and patient involvement

Lay person review of the PIS and ICF has been completed by the Edinburgh Clinical Research Facility – Covid-19 Patient Public Involvement Advisory Group. Feedback from the group has been adopted throughout these documents.

9.3 Confidentiality and data protection

The CI and study staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate study staff only. Computers used to collate personal data will have limited access measures via user name and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory

authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated study staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

9.4 Insurance and indemnity

NHS Tayside is Sponsoring the study.

Insurance – NHS Tayside will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.
Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity - The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

10 SAFETY REPORTING

As this is an observational study an adverse event in this protocol is defined as any untoward medical occurrence in a patient or clinical investigation that has occurred from research interventions only. Therefore, we will only report adverse events that relate directly to participation in the study (for example, as a consequence of providing additional blood samples, taking nasal brushing). All adverse events (AEs) will be recorded on an AE log in the ISF to capture start and end dates.

11 ANNUAL REPORTING REQUIREMENTS

An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 Protocol amendments and breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, and where appropriate, REC and R&D. Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the DMS, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a breach of GCP or protocol is suspected, this will be reported in accordance with the Sponsor SOP.

12.2 Archiving

Archiving of study documents will be for 25 years after the end of study in accordance with Sponsor SOP to allow assessment of very long-term effects of severe COVID-19 disease in later life.

12.3 End of study

The end of study will be on completion of long-term data follow up. The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 DISSEMINATION POLICY

13.1 Authorship policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated and a clinical study report will be prepared.

13.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

Participants will be informed that the study results will be published online.

13.3 Peer review

This study has been funded by the Chief Scientist Office, Scottish Government and the British Lung Foundation who have reviewed the grant application and the protocol has been approved by the Sponsor Committees responsible for this.

Resulting publications will be reviewed by the referees of the journal to which the paper (and its protocol) will be submitted.

14 REFERENCES

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