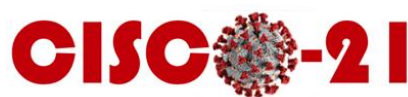


**Full Title: Prevention and early treatment of the long-term physical effects of COVID-19: a randomised clinical trial of resistance exercise.**

**Short title: CISCO-21 - Treat and Prevent Long COVID**

<b>PROTOCOL VERSION NUMBER AND DATE:</b>	<b>Version 1.1; 30/03/2021</b>
<b>IRAS Number:</b>	<b>294299</b>
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<b>Sponsors Number:</b>	<b>GN20CA537</b>

**This protocol has regard for the HRA guidance and order of content**


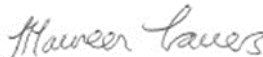


## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Good Clinical Practice (GCP) guidelines, the Sponsor's (Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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Signature: 		Date: 07/04/2021
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Position: PROFESSOR OF CARDIOLOGY AND IMAGING		
<b>For and on behalf of the Study Sponsor (NHS Greater Glasgow and Clyde):</b>		
Signature: 		Date: 07/04/2021
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## TRIAL SUMMARY

<b>Study Title</b>	Prevention and early treatment of the long-term physical effects of COVID-19: a randomised clinical trial of resistance exercise.
<b>Other Title</b>	Treat and prevent Long COVID
<b>Acronym</b>	CISCO-21
<b>Study Design</b>	Randomised, controlled, open-label, parallel group, clinical trial
<b>Study Participants</b>	Patients with confirmed COVID-19 recovering in hospital, or having been discharged or not admitted, and with persisting symptoms (4 weeks or more as per NICE guidance).
<b>Research Question/Aims</b>	<ol style="list-style-type: none"> <li>1. To undertake a pragmatic clinical trial of resistance-based exercise in addition to standard care versus standard care only to prevent and treat persisting symptoms post-COVID-19.</li> <li>2. To rapidly translate and disseminate our research findings.</li> <li>3. To develop a national platform for rapid, multicentre clinical trials post-COVID-19.</li> </ol>
<b>Eligibility</b>	<p>Patients will be classified according by clinical presentation:</p> <p>A) Non-hospitalised - Positive diagnosis with persisting symptoms for at least 4 weeks from symptoms onset leading to medical review (A&amp;E, Community COVID Hub) but not admission (Treatment group),</p> <p>B) Hospitalised, positive diagnosis, and with post-discharge, persistent symptoms for at least 4 weeks from symptoms onset (Treatment group),</p> <p>C) Hospitalised, positive diagnosis, and in convalescent phase in-hospital (preventive group).</p> <p>Groups A &amp; B = target population for <i>treatment</i> of persisting symptoms post-COVID i.e. Long-COVID;</p> <p>Group C = Target population for <i>prevention</i> of Long COVID.</p> <p><b>Inclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Virology PCR positive laboratory diagnosis of COVID-19,</li> <li>2. Within 6 months of diagnosis,</li> <li>3. Persistent symptoms for at least 4 weeks from symptoms onset (Groups A &amp; B only)</li> <li>4. Presentation type - one of group A, B or C.</li> </ol>

	<p><b>Exclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Physiotherapy as part of standard care e.g. post-ICU, post-HDU,</li> <li>2. No expectation of being able to walk within 3 months</li> <li>3. Unable to provide informed consent,</li> <li>4. Unable to comply with the protocol.</li> <li>5. Known pregnancy</li> </ol>
<b>Intervention</b>	Resistance exercise in addition to standard care
<b>Control</b>	Treatment as usual (standard care) without resistance exercise
<b>Primary outcome</b>	Incremental shuttle walk test (ISWT) at 3 months post-randomisation
<b>Secondary outcomes</b>	<ol style="list-style-type: none"> <li>1. Spirometry;</li> <li>2. Handgrip strength;</li> <li>3. Short Physical Performance Battery (SPPB)</li> <li>4. EQ5D, PHQ, Illness perception (Brief IPQ), Duke Activity Status Index (DASI), International Physical Activity Questionnaire (IPAQ-SF) short-form, Fatigue questionnaire, MRC dyspnoea score;</li> <li>5. Frailty assessed using 1) the Fried frailty phenotype: five criteria: weight loss; exhaustion; grip strength; low physical activity; and slow walking pace; 2) Clinical Frailty Scale.</li> <li>6. Episodes of care (primary, secondary, physiotherapy, rehabilitation) up to 3 months (Visit 2), and in the longer term</li> <li>7. Hospitalisation for any reason up to 3 months (Visit 2), and in the longer term.</li> </ol>
<b>Exploratory outcomes / sub-studies</b>	<ol style="list-style-type: none"> <li>1. Exercise dose achieved (1) daily log, (2) level attained and within subject change from baseline,</li> <li>2. Oxygen saturation, heart rate and respiratory rate at the start and end of the ISWT</li> <li>3. Adherence with exercise (log).</li> <li>4. Accelerometry (Glasgow only)</li> <li>5. Biobank tissues samples for biomedical research.</li> </ol>
<b>Planned Sample Size</b>	<p>220 randomised participants (n=110 per randomised group)</p> <p>Stratification of randomisation by clinical categories, A, B and C, history of COVID pneumonia, age, sex and site.</p>

<b>Planned Trial Period</b>	24 months Pre-start: secure approvals and study set up. Week 1: participant enrolment, implementation Week 52: mid-point review Week 104: final report. Record linkage for long term follow up
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## **ROLE OF STUDY SPONSOR AND FUNDER/SUPPORTER**

NHS Greater Glasgow & Clyde will be the sponsor of the trial. Sponsor will provide approvals, support regulatory submissions and ensure the requirements of the study are met as per the statement on the signature page of this protocol.

The study is funded through the Chief Scientist Office.

## **ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/ GROUPS & INDIVIDUALS**

### **Trial Management Group (TMG)**

The study will be coordinated from NHS Greater Glasgow & Clyde (NHS GG&C) by the Study Management Group (SMG). The SMG will consist of the chief investigator, project manager and representatives from both NHS GG&C and other organisations relevant to the study. The role of the group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

### **Trial Steering Committee (TSC)**

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will:

- review the trial protocol and agree substantial protocol amendments
- provide advice to the investigators on all aspects of the trial
- include an independent chairperson, at least 2 other independent members, and the Co-sponsor and a patient or carer representative

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the sponsor. The TSC will meet at the start of the study, and 6-monthly thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

### **Independent Data Monitoring Committee (IDMC)**

An IDMC will be established to include a minimum of two independent medical experts (covering cardiovascular disease and/or COVID-19; one of the academic clinicians will act as chair) and an independent biostatistician. The Glasgow CTU will liaise with the committee and ensure that the committee is provided with adequate information about study progress and results.

The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Glasgow CTU and the co-sponsors. Responsibilities include:

- To protect the safety of patients recruited to the trial.
- Advising the TSC and sponsor if it is safe and appropriate to continue with the study.
- Examining information provided by the Glasgow CTU on study recruitment, adverse events and outcomes and providing recommendations for the Project Office to forward to the TSC, ethics committees, regulatory bodies, study sponsors, and the funder.

The IDMC will receive unblinded reports on study safety data and on study progress and outcomes. The IDMC may recommend to the TSC and co-sponsors that the study should stop prematurely because of concerns about patient safety. The IDMC will meet approximately every six months. No formal interim analyses are planned. The IDMC will take into account all of the results and the consistency and biological plausibility of the findings. These analyses will have no impact on the required sample size for the study.

## **PROTOCOL CONTRIBUTORS**

The protocol has been developed by a group with extensive clinical and research experience relevant to this study – our list of contributors can be found on Pages 4 and 5 of this protocol. The team includes internationally leading experts in clinical trials (Berry, Cleland, Lang, Sattar, Taylor), biomarkers (Goodyear, Sattar), pulmonary rehabilitation (Anderson, Bayes), exercise physiology (Gray), primary care (Mair), and biostatistics (McConnachie).

The study will be supported by the Robertson Centre for Biostatistics, University of Glasgow and Clinical Research & Development and the Project Management Unit, NHS GGC.

## **KEYWORDS**

- Coronavirus-19 (COVID-19)
- SARS-CoV-2
- Resistance exercise
- Health status
- Exercise capacity
- Rehabilitation
- Cardiovascular disease
- Clinical trial

## LIST OF ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BMI	Body Mass Index
CA	Competent authority
CAD	Coronary artery disease
CHI	Community health index
CI	Chief investigator
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTPA	Computed tomography pulmonary angiography
CTU	Clinical trials unit
CXR	Chest X-ray
DASI	Duke Activity Status Index
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EQ5D	European quality of life 5-domain
EU	European Union
GCP	Good clinical practice
GDPR	General data protection regulation
GP	General Practitioner
ICAM	Intercellular adhesion molecule-1
ICF	Informed consent form
ISWT	Incremental shuttle walk test

ICMJE	International Committee of Medical Journal Editors
ICH GCP	International Conference on Harmonization of Good Clinical Practice

IPQ	Illness perception questionnaire
ISF	Investigator site file
LPLV	Last Patient Last Visit
LV	Left ventricle
MI	Myocardial infarction
MRC	Medical Research Council
NHS	National Health Service
NHS GGC	National Health Service Greater Glasgow & Clyde
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-brain natriuretic peptide
PCR	Polymerase chain reaction
PHQ-9	Patient health questionnaire - 9
PPI	Patient and Public Involvement
PROMS	Patient reported outcome measures
RCPGP	Royal College of General Practitioners
REC	Research Ethics Committee
SAE	Serious adverse event
SDV	Source data verification
SIGN	Scottish Intercollegiate Guideline Network
SMG	Study management group
SOP	Standard Operating Procedure
SOT	System organ term
SSI	Site specific information
RUSAE	Related Unexpected Serious Adverse Event

SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischaemic attack
TMF	Trial master file
UK	United Kingdom
ULN	Upper limit of normal
WHO	World Health Organisation

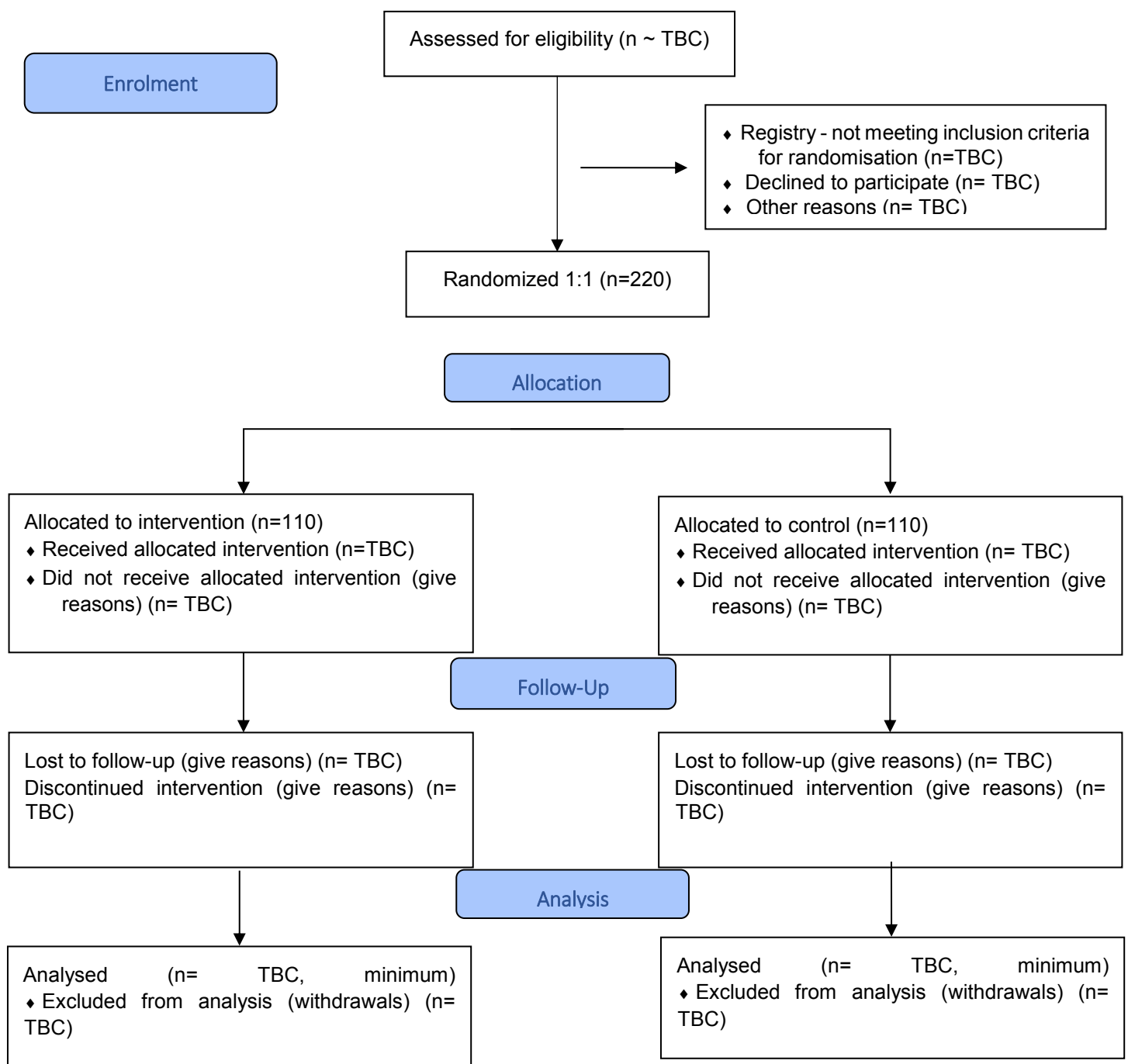
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## FLOW DIAGRAM



### CONSORT 2010 Flow Diagram





## SCHEDULE OF ASSESSMENTS

Visit	1	2	3
Timeline	Day 1	3 months (+6weeks)	E-linkage
Trial Activity	Enrolment	Outcome evaluation	1 & 10 years
Setting	Hospitalised, non-hospitalised COVID-19	CRF	
Screening – Inclusion/Exclusion Criteria including DASI questionnaire	√		
Written Informed Consent	√		
General health status check	√		
Medical History / clinical status <sup>2</sup>	√	√	
Vital signs (heart rate, rhythm, BP, height, weight, waist circumference, oxygen saturation, at baseline and during follow-up)	√	√	
Cardiovascular risk factors, risk score	√	√	
Routine blood samples as per standard of care	√	√	
Spirometry	√	√	
Handgrip strength	√	√	
Short Physical Performance Battery (SPPB)	√	√	
Accelerometer (Glasgow only)	√	√	
PROMS including EQ5D, PHQ, Illness perception (Brief IPQ), Duke Activity Status Index (DASI), International Physical Activity Questionnaire (IPAQ-SF) short-form, Fatigue questionnaire	√	√	
Frailty 1) Fried 5-criteria phenotype, 2) Clinical Frailty Scale	√	√	
Training - Hospital, CRF, on-line, telephone			
Randomisation	√		
Training (resistance exercise)	√		
Incremental shuttle walk test (ISWT)	√	√	

Exercise dose (log, level, adherence)	√	√	
Episodes of care (primary, secondary, physiotherapy, rehabilitation)		√	√
Research blood sample		√	
Data collection – clinical endpoints (collected via hospital Portal/Trakcare systems) and e-record linkage			√

All visits should be performed within the documented visit time (e.g. 3 months +6 weeks). The aim is to meet these visit windows but any that are out-with will be dealt with at the analysis stage, as appropriate, and therefore will not be considered protocol deviations. If the visit date is extended beyond 3 months, the participant should continue with the exercise regimen until the day of the visit.

1. Informed consent must be obtained before the patient undertakes any study assessments.
2. Clinical activity is defined as ‘Standard Care’(including safety), ‘Research’, or for the UK NHS, ‘NHS Support’, ‘NHS Treatment’
3. The research blood sample should be undertaken at the 3-month visit.
4. The participants will be contacted by the Research Staff by telephone one week after enrolment, regardless of the randomised group in order to assess patient wellbeing and adherence with the resistance exercise intervention. If there are concerns, then the participant will be invited to the Clinical Research Facility for review.
5. Consent covers the randomised study and participation in an optional follow-up using electronic linkage of NHS and government records for episodes of care and death (and their causes) and medication in the longer term.

Standard care blood samples e.g. FBC, U&E, HbA1c, D-Dimers, NTproBNP, lipids, CRP, high sensitivity troponin

Research blood samples: Exploratory analyses may include - Haemostasis - Claus Fibrinogen, D-Dimer, FVIII (one stage), VWF antigen, VWF:GP1ba, Antithrombin activity, Protein C activity, Free protein S; Cardiac - NT-proBNP, hs-troponin; Vascular cytokines - ET-1, ICAM, VCAM, p-selectin, IL-6, VWF, Nox3; Vascular cells and microparticles; Metabolic status - HbA1C, lipids; Blood RNA (Tempus™ or PAXgene®) including for RT-PCR of SARS-CoV-2 and RNA for vascular biology; Inflammation – hs-CRP, ST2; Immune response antibodies; Collagen metabolites; DNA - The buffy coat will be stored for DNA analysis e.g. candidate gene SNPs, other variants. Residual blood will be saved for future analyses of interest. These analyses will be undertaken in University laboratories or in laboratories of external collaborators (industry or academic, UK or abroad) by agreement with the Sponsor.

# STUDY PROTOCOL

## Prevention and early treatment of the long-term physical effects of COVID-19: a randomised clinical trial of resistance exercise.

### 1. BACKGROUND

The COVID-19 pandemic is having an unprecedented impact on our health and social services, and on the population, society, and the economy [1,2]. COVID-19 is a systemic illness, and complications include pneumonia and pulmonary thromboembolism [3]. In our CSO-funded Cardiovascular Imaging in SARS-CoV-2 (CISCO-19) study [4; pilot data], most hospitalised patients experience persisting health problems after the acute illness. COVID-19 is associated with an increase in cardiovascular risk [3-5], that potentially may be reduced by evidence-based cardiovascular interventions. A report in the BMJ (May 2020) from the ISARIC-4C framework described the results for 17,702 patients admitted to 208 acute hospitals in the UK, including several hospitals in NHS Scotland [3]. A history of cardiac disease was among the most common morbidities (31%, 5469/17702), and a multivariable predictor of all-cause mortality (hazard ratio (95% confidence interval) 1.16 (1.08 to 1.24);  $p < 0.001$ ). These results provide a strong link between cardiovascular disease and the prognosis of COVID-19.

Systemic inflammation, direct infection of endothelial cells by SARS-CoV-2 and dysfunction of angiotensin converting enzyme-2 (ACE2), cause endothelial dysfunction (aka 'endothilitis') [4,6,7]. Consequent microvascular dysfunction, thrombosis, and occlusion likely play a key role in multi-organ dysfunction, especially in the lung, heart, and kidney. A key objective of CISCO-19 is to assess coronary microvascular function [4]. We have found that myocardial injury, such as might occur due to myocarditis, is uncommon [4, pilot data]. On the other hand, impairments in blood flow in the heart appear to affect around 1 in 3 patients, and estimated oxygen consumption ( $VO_{2max}$ ), a measure of aerobic exercise capacity, is persistently reduced during the convalescence phase (1 month) [4]. Bringing these findings together with the current published evidence, COVID-19 patients have a risk of persisting symptoms, coronary and systemic microvascular dysfunction may be an underlying mechanism for persisting exertional breathlessness, chest pain, and fatigue [4-7].

COVID-19 patients may experience a loss of metabolically active tissue [8]. Hospitalisation may be prolonged, and they are at risk of substantial weight loss, including sarcopenia and cachexia [9]. The mechanisms of cachexia are multifactorial and include tissue catabolism secondary to the acute infection, systemic inflammation, cytokine activation, and loss of mobility [10]. These problems may be especially relevant in older patients with COVID-19, and those with pre-existing chronic health problems, of whom there are many. Even a short period of immobilisation, in-hospital or at home, bed rest and the inactivity of sustained quarantine can have clinically relevant effects on muscle and metabolic health. A reduction in physical activity for just 2 weeks can result in significant losses in muscle mass and function [11] and peripheral insulin sensitivity [12]. A systematic review has identified generalised impairments in physical function after COVID-19 [13]. This is important, as muscle mass is a strong predictor of prognosis in many chronic conditions, and frailty, which associates with multimorbidity and socioeconomic deprivation, may be especially relevant [14].

Pharmacological methods to increase muscle mass are few and the main method to improve muscle mass and function is via resistance exercise. We have recently developed a resistance exercise intervention [15] which we have employed in people with type 2 diabetes (see pilot data). On top of its effects on muscle mass and function, which are not seen with other forms of exercise, resistance exercise is pragmatic in COVID-19 as it can be easily adapted to the patients' capabilities and

performed in patients from the spectrum of bed-bound to ambulatory with the need for little equipment. Resistance exercise has similar broad ranging health benefits, such as reducing blood pressure and improving glycaemic control (PMID: 30045740; 30969369) and be associated with a reduction in CVD risk (PMID: 30376511). Importantly for this study, resistance training during periods of reduced activity can attenuate the declines in muscle mass and function (PMID: 26265753).

Many patients who have survived COVID-19 describe persisting health problems. NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) have defined Long COVID as 'signs and symptoms that develop during or following an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis' [16]. Using clinical data from the over four million people who downloaded the COVID Symptom Study app [17] developed by the health science company, ZOE, Spector and colleagues at Kings College London have provided insights into persisting health problems of COVID-19 patients who were not admitted to hospital. Their preliminary and, arguably, somewhat 'crude' data show that more than 1 in 8 individuals still have problems after one month from the date of diagnosis, around 1 in 20 have persisting symptoms at two months and 1 in 50 have symptoms at 3 months. Given the scale of the COVID-19 pandemic, many thousands of individuals will be affected. These Long COVID sufferers reported a range of symptoms, including up to 20 different symptoms beyond those used for the initial diagnosis of acute infection. These results underline that COVID-19 is a multisystem disease that requires a multidisciplinary approach to treatment.

Since SARS-CoV-2 is a new virus, the initial research focus has been to investigate the acute illness through observational studies and trials of acute therapy. In the CSO Rapid Research programme, we secured funding for the CISCO-19 heart, lung, and kidney imaging study (ClinicalTrials.gov Identifier: NCT04403607) based in the West of Scotland [4]. This on-going study involves recruiting 160 patients in hospital, imaging at 28 days post-discharge and then again at 1 year. The study involves stress perfusion cardiovascular magnetic resonance (CMR) to quantify myocardial blood flow, and CT coronary angiography (CTCA). Patient reported outcome measures (PROMS), covering symptoms, quality of life, and functional status), and blood samples are being collected at each visit. COVID-HEART, a national BHF-NIHR Flagship study, was modelled on CISCO-19. These, and other BHF-NIHR studies, will describe the natural history of COVID-19. ISARIC-4C is a UK-wide, secondary care COVID-19 study [3]. PHOSP is a national consortium funded by the UKRI studying long-term health outcomes in patients who have been hospitalised for COVID-19. PHOSP involves 3 tiers, including routine clinical data (Tier 1), research assessments measured at standard care clinic visits (Tier 2; n=4,000 patients) and de novo, linked studies (Tier 3). The PHOSP Tier 2 assessments may occur at 6 weeks (phone call), 3 months (the first face-to-face consult), and 6 and/or 12 months, where clinically indicated. In the main, these national flagship projects have focused on characterisation of the disease and implementing frameworks to support research. To date, randomised trials have focused on the acute phase of the illness. They include RECOVERY (NCT04381936), TACTIC-E (NCT04393246) and DEFINE (NCT04473053).

Clinical management of patients following COVID-19 in the NHS will generally align with practice guidelines from the British Thoracic Society and other key stakeholders such as NICE, RCPGP and SIGN. Local practice may vary according to circumstances. In NHSGGC, patients who have been admitted with radiological and/or virology confirmed COVID-19 would be invited for a CXR 12 weeks post-discharge and if there are persisting abnormalities on the X-ray, the patient would be invited to a phone consultation. Patients would attend out-patient clinics according to clinical need and logistical considerations.

As we learn more about the natural history of COVID-19, it is clear that many patients (millions worldwide) are left with persisting symptoms such as exercise intolerance, breathlessness, fatigue, [3,4,17] that may represent persisting dysfunction of the heart, lungs, peripheral tissues, and their

microcirculation [3,4]. It is also possible that COVID-19 was just an intercurrent event that interacted with and exposed an underlying health problem (e.g. chronic lung disease, or iron deficiency). A post-viral syndrome that might be anticipated to affect some patients, as is the case with other viral illnesses, is also relevant. NICE, SIGN and RCGP have highlighted the paucity of randomised trial evidence to show whether treatment of the convalescent phase after COVID-19, with or without hospitalisation, reduces longer-term disability [16]. We believe there is a knowledge-gap relating to the prevention and early treatment of longer-term health problems post-COVID-19. The recent CSO call into the long-term effects (LTE) of COVID-19 presents an ideal opportunity to build on CISCO-19. We will develop a clinical trial which in turn will set the framework for additional, linked clinical trials for national implementation across NHS Scotland, and potentially the UK. Our CSO LTE trial proposal complements our parallel application for BHF-NIHR flagship prioritisation for a “COVID-19 Rapid Cardiovascular Trials Platform” (under review, submission October 30, 2020).

## **2. RATIONALE**

Many people have long-lasting symptoms after COVID-19, such as breathlessness, fatigue and chest pain. So far, research studies of treatments for COVID-19 have focused on the life-threatening acute illness; few studies look at treatments to improve long-term health after COVID-19. COVID-19, particularly when this requires a hospital admission, can lead to weight loss and muscle wasting, contributing to worse outcomes. Muscle strengthening (resistance-based) exercise could improve outcomes in the long-term.

The rationale for our study has two main parts. The first (primary) addresses a gap in therapy, notably, for a non-pharmacological intervention. To address this gap, we have set out to develop a lifestyle intervention that may be helpful to patients with persisting symptoms in the recovery (or convalescence) phase after COVID-19. Specifically, we will train participants to undertake a pragmatic resistance-based exercise intervention that they can learn and apply according to their circumstances in-hospital or in the community. The rationale is predicated on providing patients with a personalised therapy option and empowering them in the self-management of their recovery following illness due to COVID-19 infection.

The second area of need is the general lack of evidence-based medicines for patients who have persisting symptoms after COVID-19. To address this gap, there is a need for rapid trials to evaluate multiple therapeutic candidates to urgently provide doctors (and their patients) with clinical evidence to inform treatment decisions. To address this gap, we aim to create a platform for rapid trials of new treatments after COVID-19. We wish to seize the opportunity afforded by this trial to set-up a transferable framework for future trials in COVID-19. The rationale is to provide a low-cost trials resource to facilitate the rapid set-up and cost-efficient delivery of multiple other trials. This will be a parallel work strand during the trial. We will develop a Working Group of stakeholders from across the NHS and Universities in Scotland and our COVID-19 PPI Group (which includes co-applicants and collaborators). Key considerations include repurposing novel therapy, potential for efficacy, safety, endpoint, sample size, feasibility interim analyses, power, MHRA and costs. As part of the plan of work in application (Aim 3), the researchers and PPI Group will scope these potential interventions within the context of a platform trial with a view to identifying candidates to follow-on after the exercise intervention trial. This will cut the costs of doing future trials and allow more patients the opportunity to contribute to medical research that will improve outcomes for people recovering from COVID-19.

Our team is multidisciplinary, multi-ethnic, gender-balanced and drawn from across NHS Scotland, and the University of Glasgow. We are currently leading the CISCO-19 study (ClinicalTrials.gov Identifier: NCT04403607), funded by the CSO, in the West of Scotland, using medical imaging of the hearts, lungs, and kidneys of patients, to understand the impact of COVID-19 [4]. We have consulted with members of the public, including people with COVID-19, in designing this study.

We will also undertake exploratory research into the vascular biology of COVID-19 infection. This work will be undertaken in collaboration with scientists in the University of Glasgow, including ICAMS and the MRC Centre for Virus Research. A blood sample at 3 months will be collected and stored in the NHS Biorepository.

In order to assess the natural history, longer-term follow-up for health outcomes will be undertaken using electronic record linkage to patient records omitting the need for participants to undergo further research visits after the end of the trial. If after initial analysis longer term, follow up via national records is felt to be worthwhile additional funding will be sought for this.

### **Alignment with other national / international initiatives**

Our Tier 3 PHOSP proposal is intended to link with COVID-HEART and other studies in NHS Scotland that include consent to be contacted about future research. Co-enrolment would be desirable to synergise the studies. If funded, our trials programme will bring in new resource to enhance enrolment into existing studies, specifically, by engaging more sites, and more research staff. The primary outcome of the exercise intervention coincides with the Tier 2 visit in PHOSP. Our consortium includes the lead investigators of BHF-NIHR prioritised studies. Prof Berry contributed to the concept and protocol of COVID-HEART. He is PI for CISCO-19, a Trial Steering Committee member of PHOSP and Co-Local PI for CAPACITY-COVID.

### **Future trials**

Our proposal will create a trials framework ready for use in real-time with the potential to extend and develop contingent on future research funding. Having set up the multicentre clinical trial, we wish to make available the framework to support other interventions (see below). They are anticipated to include interventions for which substantial safety data already exist but for which efficacy data are lacking in this patient population. Developing these new trials, from concept through to funding, is a specific aim that is nested within the current proposal. This plan builds on the existing infrastructures already in use for CISCO-19 and other COVID-19-related research developed by clinical researchers at the Universities of Glasgow and Dundee. The proposal will link with existing, national research studies including the BHF-NIHR prioritised COVID-HEART and PHOSP studies in which the CI (Berry) already has leadership roles (Co-Lead, COVID-HEART; TSC Member, PHOSP), and potentially facilitate a UK wide trials platform. Our vision is to provide other researchers with an eCRF that is already immediately available for use. The eCRF platform would then be customised to the needs of the study. This approach should facilitate rapid set up of multiple new trials and greatly reduce costs.

### 3. RESEARCH QUESTION / AIM(S)

#### 3.1 Objectives

- 1) To undertake a clinical trial of pragmatic resistance-based exercise in addition to standard care versus standard care only to prevent and treat persisting symptoms post-COVID-19.
- 2) Rapidly translate and disseminate our research findings.
- 3) Develop a national platform for rapid, multicentre clinical trials post-COVID-19.

#### 3.2 Questions

1. **Does resistance-exercise intervention improve functional capacity and health status post-COVID-19?**  
Hypothesis: A personalised yet pragmatic approach to resistance-based exercise as an adjunct to standard care improves health status and functional capacity, as compared to standard care without resistance-based exercise.
2. **Do the results of this trial elucidate mechanisms of disease in Long COVID?**  
Hypothesis: Improvements in functional capacity with resistance-based exercise identify *reversible impairments* in skeletal muscle function in patients after COVID-19.
3. **Is a national clinical trials platform for post-COVID patients in NHS Scotland feasible?**  
Hypothesis: A clinical trials infrastructure permits the rapid implementation of novel therapeutic interventions in patients with Long COVID.

#### 3.3 Primary outcome

Incremental shuttle walk test (ISWT) at 3 months.

Incremental shuttle walk test (ISWT) [20]. This is a validated measure of functional capacity, with test-retest reliability and evidence of being responsive to rehabilitation interventions. The ISWT is used as a Tier 2 evaluation in the PHOSP-COVID study. By adopting the ISWT as the primary outcome measure, our study will complement PHOSP, align with the protocol (for those patients who have been enrolled), and potentially, enhance co-enrolment into this observational study.

Oxygen saturation, heart rate and respiratory rate will be measured at the start and end of the ISWT. They will be exploratory outcomes.

### 3.4 Secondary outcomes

1. Spirometry;
2. Handgrip strength;
3. Short Physical Performance Battery (SPPB)
4. EQ5D, PHQ, Illness perception (Brief IPQ), Duke Activity Status Index (DASI), International Physical Activity Questionnaire (IPAQ-SF) short-form, Fatigue questionnaire, MRC dyspnoea score;
5. Frailty assessed using 1) Fried frailty phenotype: five criteria: weight loss; exhaustion; grip strength; low physical activity; and slow walking pace; 2) Clinical Frailty Scale
6. Episodes of care (primary, secondary, physiotherapy, rehabilitation)
7. Hospitalisation for any reason.

The secondary outcomes are intended to align with PHOSP assessments at 3-months.

### 3.5 Exploratory outcomes

- 1) Exercise dose achieved (1) daily log, (2) level attained and within subject change from baseline,
- 2) Vital parameters of cardio-respiratory function e.g. oxygen saturation, heart rate, respiratory rate at baseline and during follow-up
- 3) Adherence with exercise (log)
- 4) Accelerometry (Glasgow site)
- 5) Biobank tissues samples for biomedical research

Research blood samples: Exploratory analyses may include - Haemostasis - Claus Fibrinogen, D-Dimer, FVIII (one stage), VWF antigen, VWF:GP1ba, Antithrombin activity, Protein C activity, Free protein S; Cardiac - NT-proBNP, hs-troponin; Vascular cytokines - ET-1, ICAM, VCAM, p-selectin, IL-6, VWF, Nox3; Vascular cells and microparticles; Metabolic status - HbA1C, lipids; Blood RNA (Tempus™ or PAXgene®) including for RT-PCR of SARS-CoV-2 and RNA for vascular biology; Inflammation – hs-CRP, ST2; Immune response antibodies; Collagen metabolites; DNA - The buffy coat will be stored for DNA analysis e.g. candidate gene SNPs, other variants. Residual blood will be saved for future analyses of interest.



## **4. STUDY DESIGN**

This trial has a prospective, randomised, open-label, parallel group design. The trial is designed to assess the superiority of resistance-exercise intervention as compared with standard care without this intervention in patients recovering after COVID-19.

## **5. SETTING**

All patients presenting at participating hospitals and Primary Care settings e.g. community assessment centres (CAC), Community Health Centres (CHC) or Community Test Centres (CTC), with COVID-19 can be considered for inclusion. Also, patients enrolled in CISCO-19, OBELIX, RECOVERY and ISARIC studies, and other relevant studies, who fulfil the inclusion/exclusion criteria for CISCO-21, with the permission of the study CI and local PI, may be approached re co-enrolment in the CISCO-21 study. A screening log with the reasons for not being enrolled, will be prospectively completed.

Research collaborators include, in the University of Glasgow, the Institute of Cardiovascular and Medical Sciences, the MRC-University of Glasgow Centre for Virus Research, the Robertson Centre for Biostatistics and the Electrocardiography Core Laboratory.

### **5.1 Standard care**

Clinical management of patients following COVID-19 in the NHS will generally align with practice guidelines from the British Thoracic Society and other key stakeholders such as NICE, RCPGP and SIGN. Local practice may vary according to circumstances. In NHSGGC, patients who have been admitted with radiological and/or virology confirmed COVID-19 would be invited for a CXR 12 weeks post-discharge and if there are persisting abnormalities on the X-ray, the patient would be invited to a phone consultation. Options for the evaluation of patients with persisting symptoms include to provide an oxygen saturation monitor, a functional assessment of physical capacity, and/or an invitation to attend an out-patient clinic according to clinical need and logistical considerations.

## **6. STUDY POPULATION**

### **6.1 Clinical strata**

Since COVID-19 is an acute illness with a recovery period that may be prolonged, we recognise that different approaches are needed to reflect the stage and trajectory of recovery from COVID-19. Patients will be classified according to the clinical management of their illness:

- A. Non-hospitalised - Positive diagnosis with persisting symptoms leading to medical review (A&E, SATA, Community COVID Hub) but not admission,
- B. Hospitalised, positive diagnosis, post-discharge, persistent symptoms,
- C. Hospitalised, positive diagnosis, convalescent phase in-hospital.

Groups A & B = target population for treatment of persisting symptoms post-COVID i.e. Long-COVID;  
Group C = Target population for prevention of Long COVID.

### **6.2 Inclusion criteria**

- 1) Virology PCR positive laboratory diagnosis of COVID-19,
- 2) Within 6 months of diagnosis,
- 3) Persistent symptoms for at least 4 weeks from symptoms onset (Groups A & B only)
- 4) Presentation type - one of group A, B or C;

### **6.3 Exclusion criteria**

- 1. Physiotherapy as part of standard care e.g. post-ICU, post-HDU,
- 2. No expectation of being able to walk within 3 months
- 3. Unable to provide informed consent,
- 4. Unable to comply with the protocol.
- 5. Known pregnancy

NB Since the primary outcome is the ISWT at 3 months, a patient who will not be able to walk during the follow-up period would therefore not be able to complete the primary outcome evaluation. Accordingly, a patient who will be unable to walk should not be enrolled. Patients who are 'bed-bound' may be enrolled provided there is a reasonable belief that they will be able to walk 3 months later.

### **6.4 Stratification of randomisation**

Participants who fulfil eligibility criteria and provide written informed consent will have randomisation stratified by clinical strata groups (A – C), history of COVID-19 pneumonia (yes / no), age, sex and site.

## **7. TRIAL PROCEDURES**

Please see Schedule of Assessments

### **7.1 Screening and recruitment**

Screening will be undertaken in A&E, the Acute Medical Assessment Units and medical wards. Patients who attend Community Assessment Centres, Community Test Centres or Health Centres and have a diagnosis of COVID-19 confirmed may also participate. Patients with a history of COVID-19 who have been discharged following this episode of care may also be sent the PIS and consent form. These centres may display posters about the study such that the patients may contact the research centre if their symptoms persist during their convalescence. Posters may also be placed in public areas in the hospitals and community health centres.

A screening log will be prospectively recorded and entered into the eCRF.

Patients who are enrolled in observational studies may be eligible to participate. For example, the Cardiovascular Imaging in SARS-CoV-2 (CISCO-19) study is an observational cohort study and patients are invited to give informed consent to be contacted about future studies. Therefore, patients who have been enrolled into CISCO-19 and who fulfil eligibility criteria may be eligible to participate in this next-stage clinical trial.

### **7.2 Informed consent**

Only patients who are sufficiently well to understand the information about the study (including the potential for benefit and known risks), as described by the attending clinical research nurse and/or clinician, would be eligible to participate. Potential participants will be identified and screened using the clinical inclusion and exclusion criteria defined in this protocol, and approached as follows: Patients in

Group A - Non-hospitalised, with symptoms persisting for at least 4 weeks post diagnosis: Potential participants in this patient group will be identified and invited to take part in the study when they attend A&E or Community Assessment Centre, Community Test Centre or Community Health Centre with persistent symptoms. They can be given a PIS at this visit, or agree for their contact details to be passed on the research team and a PIS sent out to them. Alternatively, they may be identified at a later date from review of records by the usual care team and sent a letter of invitation and a PIS at this point.

Group B- hospitalised with COVID-19, with symptoms persisting for at least 4 weeks post diagnosis, and discharged. Potential participants will be approached by their usual care team re the study pre – discharge, or agree for their contact details to be passed to the research team and a PIS sent out to them. Again, if patients are identified as potentially eligible from a review of records at a later date the can be sent an invitation letter with a PIS for the study with contact details of the research team.

In groups A and B we would also like to be able to follow up the letter with a phone call after 2 weeks to see how patients are and if are interested in joining the study

Group C- hospitalised with COVID-19 and convalescent in hospital: Potential participants would be approached by a member of their usual care team re taking part in the study and if interested asked to agree to speak to a member of the research team about this.

Potential participants for all groups will be given as much time as they need to decide whether to take part in the study.

In all cases clinical staff will be available to discuss the study with the patient and his/her family and friends. If the patient agrees to take part in the study, then the consent form will be signed by the patient and the member of staff obtaining the consent. The decision to include a patient in the study will be documented in the medical notes. No further scheduled study assessments can be performed until written informed consent has been obtained.

Withdrawal criteria: A participant may withdraw from the study at any time. There are no specific withdrawal criteria, although clinicians can withdraw patients as appropriate and record the reasons. All patients will be followed up for clinical outcomes, unless consent is specifically withdrawn.

Participants consenting for the study will be invited to provide consent for long-term follow-up of their electronic medical records (with no additional patient contact). Consent will be sought to use study data in other ways such as in pooled analyses of anonymised data such as for natural history studies, meta-analyses and health outcomes research.

### **7.3 Recruitment plan**

Healthcare staff who participate in this study should adopt a consecutive approach to enrolment in order to minimise selection bias and provide a study cohort that is representative of patients treated during usual care. The results are intended to have external relevance and be transferable to clinical practice. This approach will also facilitate timely delivery of the trial.

The sample size estimate takes account of a degree of participant withdrawals from the study, incomplete data, and problems with data acquisition.

### **7.4 Clinical evaluation**

#### **7.4.1 Clinical status**

Information on medical history and COVID-19 will be collected. The information will be collected at baseline and again at 3 months. The information will as far as possible align with the CISCO-19 study (Appendix), and will include:

1. Cardiovascular history

2. Medical history/therapy, including history of COVID-19 pneumonia and physiotherapy
3. Vital signs and anthropometry (heart rate, rhythm, blood pressure, height, weight, waste circumference, oxygen saturation)
3. Comorbidity including the components of the Charlson Index
4. Scottish Index of Multiple Deprivation derived from the post code
5. Cardiovascular risk factors e.g. smoking history, cardiovascular risk scores.
6. Respiratory history – Asthma, bronchiectasis, COPD (including bronchitis and emphysema), chronic rhinosinusitis, hypersensitivity pneumonia, lung cancer, lung fibrosis, chronic pleural disease, pneumoconiosis, pulmonary eosinophilia, pulmonary vascular disease (PTE, pulmonary hypertension, cor pulmonale), sarcoidosis, sleep apnoea syndrome), other \*WHO Common Chronic Respiratory disease list.
7. Post-COVID lung disease (convalescence) - fibrosis, pulmonary hypertension, PTE
8. COVID-19 – diagnosis and treatment
9. 12-lead ECG (if available)
10. Imaging (if available) – CXR, CT chest / CTPA, cardiac
11. COVID-19 prognostic risk score e.g. ISARIC-4 and WHO severity score.

Smoking status will be defined as per established definitions:  
[https://www.cdc.gov/nchs/nhis/tobacco/tobacco\\_glossary.htm](https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm)

#### **7.4.2 Clinical strata**

For the purposes of classifying sub-groups within the target population, participants will be categorised into one of 3 groups

A) Non-hospitalised - Positive diagnosis with persisting symptoms leading to medical review (A&E, SATA, Community COVID Hub) but not admission,

B) Hospitalised, positive diagnosis, post-discharge, persistent symptoms at 4 weeks or longer (PHOSP contact),

C) Hospitalised, positive diagnosis, convalescent phase in-hospital.

Groups A & B = target population for treatment of persisting symptoms post-COVID i.e. Long-COVID;  
 Group C = Target population for prevention of Long COVID.

### **7.5 Blood Sampling**

#### **7.5.1 Sample collection**

Samples required for medical management will at all times have priority over samples taken for research. Wherever possible, taking additional research blood samples should be timed to coincide with routine clinical sampling time-points.

Sampling time-points:

Visit 1 - Enrolment (post-consent), standard care bloods (if not available),

if omitted at Visit 1,

Visit 2 – 3 months + 6 weeks following enrolment

Blood samples required at each timepoint: standard care and research samples – see footnote, Schedule of Events.

Blood samples (25 ml) for central laboratory tests of circulating molecules implicated in the pathophysiology acute MI or myocardial injury, potentially complicated by COVID-19. Sample collection kits will be provided for these research bloods, including PAXgene tubes. Samples will be collected and dealt with as per study Sample Handling Manual. These samples will be batched and analysed in line with available funding.

Routine standard of care bloods will be assayed in local NHS laboratories as per standard procedures irrespective of site. Recent publications describe cardiovascular complications leading to hospital readmissions post-COVID-19 (Ayoubkhani et al (2021); the OpenSAFELY study (Tazare J et al 2021), pointing to significant cardiovascular risk of patients with persisting symptoms.

Research samples will be handled as per instructions in Sample Handling Manual. Samples will be archived at the NHS GGC Biorepository using a LIMS. Initial exploratory analysis will be at University of Glasgow,

Results of routine blood samples will be uploaded to NHS Clinical Portal / Trakcare systems for review by clinicians.

### **7.5.2 Sample analysis**

Analysis of samples for vascular cytokines will be carried out in the Sattar/ Welsh laboratory, University of Glasgow.

The haemostasis and coagulation analyses will be undertaken in the NHS Haemostasis Laboratory (Dr Catherine Bagot), Department of Haematology, Glasgow Royal Infirmary. Immunology will be analysed in the NHS (Prof Rory Gunson) and/or University laboratories e.g. Prof Carl Goodyear, MRC CVR.

Sample collection, shipping, processing and analysis will be as per study sample manual and local SOPs

### **7.6 Oxygen saturation, respiratory rate and heart rate**

Oxygen saturation, respiratory rate and heart rate should be measured at each visit, including at the start and end of the shuttle walk test.

### **7.7 Spirometry**

Lung function should be assessed using spirometry at Visits 1 and Visit 2.

The basic measurement will be a peak expiratory flow rate (PEFR), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)

## 7.8 Muscle strength

Hand grip strength will be assessed as a measure of physical function at Visits 1 and 2. Handgrip strength will be recorded using a handheld dynamometer. For handgrip strength, measurements are performed until 3 measurements are within 5% of each other. Typically, 3 - 6 manoeuvres in each hand are performed. Responses in the dominant hand will be recorded.

## 7.9 Short Physical Performance Battery (SPPB)

The SPPB is a series of brief, simple physical tests including of the ability to stand for 10 seconds with the feet in 3 different positions (together side-by-side (score 0 – 1), semi-tandem (score 0 – 1), and tandem (score 0 – 2)), two timed trials of a 3m or 4m walk (fastest recorded) and the time to rise from a chair 5 times. The score ranges from 0 to 12 (higher scores reflect better extremity function). The gait and chair subtests score from 0 to 4.

SPPB will be supported by an SOP that takes account of information, training and standardisation.

## 7.10 Accelerometer

Accelerometry reflects body motion during daily activities. In a sub study focused to participants in Glasgow (Groups A and B), a portable accelerometer, styled as a watch, will be provided at baseline and again 3 months. An all-comers approach will be adopted with invitation to consecutively presenting patients. The device should be worn for 7 days lead.

GENEActiv accelerometer will be used and supported by a SOP with instructions and contact details if there are any issues. Of the available variables, the following are the parameters that will be obtained using the information collected via these devices:

- Total Physical activity
- Light Intensity Physical Activity
- Moderate Intensity Physical Activity
- Vigorous Intensity Physical Activity
- Sleep duration
- Sleep efficiency

## 7.11 Questionnaires

Patient reported outcome measures will be collected at each visit in order to assess their associations with the measurements (parameters) of cardiopulmonary injury / function. This would be with the intention to gain insights into the clinical significance of the research findings, and to assess temporal changes over time.

- EQ-5D: Health status and quality of life
- Anxiety/depression (PHQ4)

- Illness perception (Brief IPQ): Describes the participants self-reported health burden and perception
- Duke Activity Status Index (DASI): To assess the functional status (exercise capacity); this index is validated against the Bruce treadmill exercise test, and both are prognostically validated.
- International Physical Activity Questionnaire (IPAQ-SF): provides information on current / recent activity levels.
- Fatigue questionnaire.
- MRC Dyspnoea score.

### 7.12 Frailty

Frailty will be assessed using two scales, 1) the Fried frailty phenotype, five criteria: weight loss; exhaustion; grip strength; low physical activity; and slow walking pace (Appendix) and 2) the Clinical Frailty Scale. The Fried frailty phenotype includes distinct components whereas the Clinical Frailty Scale is a simple ordinal score that is more straightforward to complete. There is no frailty threshold for inclusion in the study, aside from the eligibility criterion that the patients should be able to walk.

### 7.13 Randomisation

Participants will be randomly assigned (1:1) to the intervention or control group. The randomisation sequence will be pre-determined before the start of the trial.

Participants who fulfil eligibility criteria and provide written informed consent will have randomisation stratified by group (clinical strata, Group A, B or C; see section 7.4, above).

The randomisation procedure will be undertaken by trained staff will use a web-based randomization tool hosted by the CTU.

### 7.14 Resistance exercise intervention

**Intervention** = a resistance-based exercise intervention for patients during the convalescence phase in-hospital through to 3-months post-discharge, a duration reflecting chronic, maintenance treatment studies. To maximise enrolment of eligible patients, the intervention may be initiated in-hospital or in the community post-discharge. Resistance bands may be used according to the exercise guideline.

Patients recovering from COVID-19 may spend many days in-hospital leading up to discharge. Patients will be placed within one of three broad categories of baseline physical capabilities (bed bound, up-to-sit, and ambulant) at the beginning of the intervention. Within the latter 2 categories, there will be progression of effort options and patients will be able to move between (up or down) these three categories.

The exercise regimens are generic and designed not to require expert physiotherapy input, therefore, the availability of NHS physiotherapists, which may be at times limited, will not be a barrier to implementation. If the study was successful it is hoped it could be adopted by ward staff. Progress will be reviewed and changes in the exercise plan will be adjusted according to a standard operating



procedure. The participants may progress through the physical capability groups during the recovery phase from their illness.

#### Peripheral locomotor muscle training

Participants will be invited to train daily. Patients will be invited to perform the number of repetitions that leads to a validated resistance exercise specific Rating of Perceived Exertion (RPE) of 8-10 (PMID: 12569225). The use of RPE to prescribe and progress resistance exercise has been shown to be as efficacious as other more complex methods but reported to be the most tolerable and enjoyable method (PMID: 31107348). Once patients can reach 15-20 repetitions of each exercise they will be advised to move to the next level within each category and once able to do this for the top level within the category, to move to the next category. Similarly, if patients are not able to manage 5 repetitions of each exercise they will move down a level and, if at the bottom level within a category, down a category.

The overall exercise programme pack is provided a single document. The exercise programme has been developed by Dr Stuart Gray (Physiologist, University of Glasgow) with guidance from our PPI group (Dr Tracy Ibbotson, Prof Frances Mair, Primary Care), Drs Hannah Bayes and David Anderson (Rehabilitation, NHSGGC), Prof Rod Taylor (MRC Unit) and Clare Burke and David Boiskin (Physiotherapy, NHSGGC QEUH).

A training package will be provided to the site research staff (research nurses, fellows). The pack will be given to patients during an initial face to face session where the nurse/therapist will help to select the most suitable category and level of exercise for the patient, and to demonstrate these and ensure patients are comfortable performing the exercises. Every 2 weeks a member of the research team will contact the patients to ensure they are happy with the exercises and to help overcome any issues that have arisen. If the patient is in hospital, the contact may be daily, as needed.

Implementation at sites will be overseen and supported by a Working Group that includes these colleagues in an advisor role. The site research staff will be trained on the practical aspects of the exercises. Training will be given through in-person site visit.

Intervention group: An instructional pack (with video links and pictures) and an exercise log will be provided to empower each patient. We have put together a draft of the exercise programme pack for patients. This has been reviewed by our PPI group (4 Nov 2020) and feedback incorporated to reflect co-design of the programme. Based on our experience in the CISCO-19 study, we believe the exercise intervention will be feasible for most patients who have capacity to follow and adhere to verbal and/or written instructions. We aim for a widely generalisable intervention that can be taken up by most post-COVID-19 patients.

The programme is intended for patients in-hospital or at home and allowing for transition between the two. Our exercise intervention is supported by a systematic review of resistance training [18]. Specific protocols [15]: taking account of feedback to ensure simplicity, safety and remove barriers to implementation, household objects e.g. bottle of water, tin of food, which would be available to all participants, or exercise tension bands are also an option, according to patient preference. This demarcates our intervention from Physiotherapy and can be facilitated by other healthcare staff including nursing staff (hospital-based, community) and medical staff (including GPs).

**LONG COVID-19 EXERCISE MANUAL** (developed by Dr Stuart Gray, Prof Colin Berry and informed by feedback from the NHS GGC Patient Group, October – November 2020),

**SUMMARY:** Exercises are personalised options according to the circumstances of the individual patient: *Bed-bound, up-to-sit, ambulant*. The resistance exercise options are described in a manual.

**Setting:** Hospitalised patients, in their room on the ward and continued until post-discharge up to 3 months. Participants may be recruited post-discharge and would then come to hospital for consent and baseline assessment and thereafter would carry out exercises at home.

**Timing and duration of interventions:** Convalescence phase through to 3 months post-discharge. This time window is intended to follow-on from the acute therapy (and trials). The window focuses on the period when patients are recovering on the medical wards, through to 3 months post-discharge, which is when the first clinical assessment takes place in PHOSP (Tier 2). Our observations from the current landscape of clinical trials in the UK is that this time-period is not fully covered by the existing studies, hence our strategic focus for this enrolment window (post-ICU/HDU through to 3 months), which is a critical time for patients in their paths to recovery. Informed consent into our trial will complement co-enrolment into PHOSP (which is an observational study).

Patients who have been treated in ICU or HDU receive Physiotherapy as part of standard care, therefore, these patients would only be eligible for enrolment if the physiotherapy has completed. This reflects our plan for 'prehabilitation' without overlap with standard care NHS Physiotherapy. The focus for our trial(s) would mainly be during the post-ICU period to post-discharge e.g. 3 months (Tier 2, PHOSP), and options for longer term follow-up assessments, also aligned with PHOSP, will be feasible. Our aim is to synergise with PHOSP (aligning timing and endpoints), enhance enrolment and the compliance with follow-up.

### **7.15 Incremental shuttle walk test**

Primary outcome: Incremental shuttle walk test (ISWT) [20]. This is a validated measure of functional capacity, with test-retest reliability and evidence of being responsive to rehabilitation interventions. The ISWT is used as a Tier 2 evaluation in PHOSP. By adopting the ISWT as the primary outcome measure, our study will complement PHOSP, align with the protocol (for those patients who have been enrolled), and potentially, enhance co-enrolment into this observational study. Use of ISWT should be registered with the University of Leicester (Prof Sally Singh), including use of the digital timer for the test. Our staff have local experience since the PHOSP-COVID study is running in Dundee and Glasgow.

Oxygen saturation, heart rate and respiratory rate at the start and end of the ISWT, and reflect exploratory outcome measurements.

### **7.16 Data Retrieval and eCRF Input**

A study clinician and/or delegated member of staff will be responsible for accessing the relevant patient data (A&E admission paperwork, discharge paperwork) and blood sample results on the NHSGG&C hospital systems, including Clinical Portal and/or Trakcare. The data provided on these systems will be considered as source data.

Patients will be allocated a unique patient number at the point of consent, and this is how they will be identified within the eCRF.

The eCRF will be developed and managed by the Robertson Centre for Biostatistics.

### **7.17 Record linkage**

Patient contact is necessary for the study visits which will be minimised by telephone contact during the study period. At the other time-points, patient contact will not be necessary if access to electronic medical records is feasible and the data are clear. When patient contact is unsuccessful the GP may be contacted, and electronic health records will be checked including for the assessment of events, and medication use in the longer term. The follow-up will be by telephone, or by letter or clinic review as clinically appropriate.

In the longer term, additional follow-up of health outcomes, and related health information e.g. primary care attendances, pharmacy prescriptions, will be assessed by electronic case record linkage using the Community Health Index (CHI) number in Scotland.

Episodes in primary and secondary care, death, and causes in primary and secondary diagnostic positions, will be assessed using electronic health records held by the NHS and government / public sector agencies.

## 8. SAFETY REPORTING

### 8.1 Definitions

#### 8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a trial specific procedure has been administered, including occurrences which are not necessarily caused by or related to that trial specific procedure.

#### 8.1.2 Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

- a) Results in death
- b) Is life threatening
- c) Requires hospitalisation or prolongation of existing hospitalisation
- d) Results in persistent or significant disability or incapacity
- e) Consists of a congenital anomaly or birth defect
- f) Is otherwise considered medically significant by the investigator
- g) Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

#### 8.1.3 Related Unexpected Serious Adverse Event (RUSAE)

Any SAE thought to be related to a trial specific procedure performed on that subject that is thought to be unexpected; that is the event is not listed within the protocol or would not be expected to occur when carrying out the trial specific procedure in normal clinical practise.

### 8.2 Serious adverse event recording and reporting

Where an SAE requires recording; full details including the nature of the event, start and stop dates, severity, relationship to research product and/or trial procedures, and the outcome of the event will be recorded in the patient's medical notes and CRFs. These events will be monitored and followed up until satisfactory resolution and stabilisation.

Each SAE should be assessed to determine if related to the research specific procedures and assessed for expectedness. Where an event meets the criteria of an SAE and is both:

- **Related:** that is, it resulted from any of the research procedures, **AND**
- **Unexpected:** that is against the procedure events listed below as an expected occurrence.

The SAE meets the criteria of a Related and Unexpected Serious Adverse Event (RUSAE) and is subject to expedited reporting to the Sponsor.

### **8.3 Expected Events Related to Phlebotomy Procedures**

There is little risk to participants taking part in this study; however, there may be complications relating to the phlebotomy procedures such as:

- Haematoma
- Nerve injury
- Arterial puncture - If this occurs, remove the needle and apply direct pressure for at least 10 minutes; if a pulsatile mass persists, consider arterial duplex ultrasonography
- Syncope
- Phlebitis or cellulitis

These events would be considered expected within this study.

### **8.4 Expected Events related to resistance exercise**

Complications of exercise intervention may be soft tissue strain, falls or exhaustion.

### **8.5 Reporting to the Sponsor**

All RUSAEs must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the generic non-CTIMP SAE form which is available from [http://www.glasgowctu.org/data/SAE\\_non-CTIMP.pdf](http://www.glasgowctu.org/data/SAE_non-CTIMP.pdf). The SAE form should be completed and signed by appropriately delegated staff. If necessary, a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with an electronic report.

If all of the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

### **8.6 Reporting of RUSAEs to the Ethics Committee**

The PV office will report all RUSAEs to the ethics committee within 15 days of the PV office becoming aware of the event, via the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site. <http://www.hra.nhs.uk/documents/2015/02/safety-report-form-non-ctimp.docx>. The form should be completed in typescript and signed by the Chief Investigator.

### **8.7 Pregnancy reporting (site responsibilities)**

Pregnancy is an exclusion criterion. If after enrolment the participant becomes pregnant, this is not considered an AE or SAE in this trial unless a negative or consequential outcome is recorded for the mother or child/foetus. However, the patient would then be invited to withdraw from the study. If the outcome meets the serious criteria, this would be considered an SAE and must be reported as per SAE reporting procedure above.

## **8.8 Recording and reporting of SAEs where eCRF access is not possible**

If recording in the eCRF is not possible a paper SAE form should be completed:

- The SAE form is downloaded from [www.glasgowctu.org](http://www.glasgowctu.org), printed off, completed and signed. The form is then faxed to the Glasgow Clinical Trials Unit Pharmacovigilance (PV) Office on +44(0)141 357 5588. If faxing is not possible a copy of the SAE form should be scanned and emailed to: [pharmacovig@glasgowctu.org](mailto:pharmacovig@glasgowctu.org). If this website is unavailable a paper copy of the SAE form is filed in the Investigator Site File at each site.
- If necessary a verbal report can be given by contacting the PV Office on +44(0)141 330 4744. This must be followed up as soon as possible with an electronic or written report.

## **8.9 Responsibilities for Safety Reporting and Review**

This section details the responsibilities for reporting and reviewing safety information arising from the trial.

### **8.10 Data Centre**

The study Data Centre will:

- Provide an eCRF for central data collection of AEs and SAEs;
- Provide reports to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and/or Trial Steering Committee (TSC)).

### **8.11 Principal Investigator (PI)**

- Checking for SAEs when participants attend for treatment / follow-up.
- Ensuring that SAEs are recorded in line with the requirements of the protocol.
- Ensuring that all SAEs are recorded in the eCRF within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Using medical judgement in assigning seriousness, causality, severity and expectedness with reference to the trial protocol and Reference Safety Information.

### **8.12 Chief Investigator (CI)**

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Using medical judgement, confirm seriousness and causality and confirm expectedness of SAEs.
- Immediate review of life-threatening SAEs

### **8.13 Sponsor**

- Verification of data collection, SAEs, according to the trial protocol
- Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit

- Preparing in collaboration with the CI the annual safety report to the Research Ethics Committee and until the End of the Study, at which time an End of Study form will be submitted.

#### **8.14 Trial Steering Committee**

In accordance with the Charter for the TSC, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues.

#### **8.15 Independent Data Monitoring Committee**

The IDMC will develop and agree a charter in line with the DAMOCLES guidelines. In accordance with the Charter, periodically reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor.

## **9. Statistical Analysis**

### **9.1 Statistical analysis plan**

This study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be authored by the Trial Statistician before unblinded data are seen.

### **9.2 General considerations**

The statistical Analysis Plan (SAP) will be based on intention to treat principles in line with CONSORT guidelines. The analysis will focus on estimation of treatment effect differences with 95% CIs and p-values. All pre-specified secondary outcome analyses will be reported in study publications.

### **9.3 Primary efficacy analysis**

Alternative hypothesis: In patients with persisting symptoms during the convalescence phase after COVID-19, resistance exercise increases exercise capacity measured by the incremental shuttle walk test. The null hypothesis reflects no difference in exercise capacity between the groups.

#### **9.3.1 Primary outcome**

Incremental shuttle walk test at 3 months

#### **9.3.2 Primary analysis and sample size**

The minimum clinically important between-group difference in the ISWT at follow-up (3 months) = 79 m, SD=105 [20], sample size for 80% power, 5% significance, no loss to follow-up (LTFU) = a minimum of 85 / group; allowing for LTFU and incomplete data, the sample size is n=110/group (n=220 total).

After 50% of the patients have been recruited, if enrolment rates and the budget permit, we will seek approval from the trial committees and Sponsor to upscale to 90% power. For 90% power, n=318/group, or 398 patients would be needed, allowing for up to 20% attrition. If enrolment rates are sufficient we will seek IDMC approval to upscale to 90% power.

### **9.4 Software and statistical analysis**

Continuous outcomes will be analysed where data are approximately normally distributed and where baseline levels are available for adjustment. Where this is the case, two sample t-tests and



corresponding confidence intervals will be used. Where data are clearly not normally distributed (e.g. laboratory variables) standard transformations will be applied to achieve approximate normality prior to analysis.

Clinical data will be made available to the data coordinating centre (the Robertson Centre for Biostatistics) through the web-based eCRF. The RCB is UKCRC-registered Clinical Trials Unit (number 16). The statistical software to be used will be SAS and/or R.

All analyses will be governed by a Statistical Analysis plan, to be finalised prior to database lock, and prior to sharing of any summary results. This plan will summarise the types of methods to be used for each study hypothesis, allowing some flexibility in the precise methods to be used, given the exploratory nature of the study.

## **10. DATA HANDLING**

### **10.1 Case Report Forms / Electronic Data Record**

An electronic case report form (eCRF) will be used to collect study data. The eCRF will be developed by investigators in the University of Glasgow and access to the eCRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the eCRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

The data management plan will inform sharing and access to bone fide researchers and a standard research agreement. Individuals/centres will be recognised through publications (acknowledgement and named authors in line with their contributions).

### **10.2 Data Retention**

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with EU GCP guidance, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 10 years after the end of the study.

## **11. MONITORING, AUDIT & INSPECTION**

NHSGGC conducts monitoring and/or audit of studies on a risk basis and in accordance with local Standard Operating Procedures. The level, frequency and priorities of monitoring and/or audit will be agreed with the NHS Governance Manager.

## **12. ETHICAL AND REGULATORY CONSIDERATIONS**

### **12.1 Research Ethics Committee (REC) review & reports**

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion (it is noted that amendments may also need to be reviewed and accepted by the NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within 6 months after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

### **12.2 Peer review**

The study design has benefitted from peer review through the Glasgow CTU, NHSGGC Patient and Public Involvement (PPI) group and the Chief Scientist Office of the Scottish Government (November – December 2020).

### **12.3 Public and Patient Involvement**

Patient and public involvement (PPI) is led by Dr Tracy Ibbotson, of the Scottish Primary Care Research Network, who steers a patient group in NHS Glasgow. This group has been actively involved in the development of our proposal.

We will establish a PPI group of patients who have had lived experience of COVID-19. They will participate in PPI activities including the design of patient packs, linking to appropriate patient groups, and co-producing written reports for patient websites and conferences. Given the level of public interest, we anticipate sharing information about our study through the media e.g. BBC, newspapers with coordination by NHS GGC and University communications teams.

Our PPI group will meet every 3 months to oversee the study and funding is included in our budget. Constituting this group at the outset of the study will also be a deliverable and the reports (minutes) from each of the meetings (scheduled to correspond with the timelines/milestones).

PPI in our research will include a patient representative on the TSC.

## **12.4 Regulatory Compliance**

The trial will not commence until full approval has been granted by the Research Ethics Committee, the R&D Management Office and Sponsor.

For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D).

## **12.5 Protocol compliance**

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

## **12.6 Notification of Serious Breaches to GCP and/or the protocol**

A "serious breach" is a breach which is likely to affect to a significant degree –

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

If any of the above occurs, then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

## **12.7 Data protection and patient confidentiality**

All investigators and trial site staff must comply with the requirements of applicable data protection legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of such legislation.

Personal information will be collected via the eCRF to enable record linkage to be carried out and to provide electronic access to study monitors to a copy of the signed informed consent document. These data items will be encrypted and only those individuals who require to see these data i.e. the person performing the record linkage and site research team staff or the study monitor, as appropriate, will be able to view them. All electronic data will be held securely in accordance with ISO 27001:2013 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.

The trial data managers, statisticians, or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.

Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data. Patient consent forms will be stored at the study site in a secure location accessible only to study teams.

### **12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management**

A log of financial or other competing interests for the CI, PIs and committee members will be held centrally by the Trial Coordinator throughout the trial. The Trial Coordinator will request this information at the site initiation visit and at regular intervals during study conduct, and it will be made available to the Sponsor.

### **12.9 Indemnity**

The NHS Indemnity Scheme will apply to this study to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

The University of Glasgow Clinical Trials Insurance will apply to this study to meet the potential legal liability for harm to participants arising from the design of the research.

The sponsor has not made any arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises. University of Glasgow insurance is also relevant.

### **12.10 Amendments**

Any change in the study protocol will require an amendment. Any proposed substantial protocol amendments will be initiated by the CI following discussion with the Sponsor and TSC and any required amendment forms will be submitted to the, ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC, and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol amendments.

### **12.11 Post-trial care**

At the end of the trial, participants will be returned to usual care as defined by local and national guidelines at that time.

### **12.13 Access to the final trial dataset**

During the trial and in the period prior to publication of the main study results as described in the protocol, only the Glasgow CTU will have access to the full dataset. After that period, the Trial Steering Committee will conduct further data analyses for a period of three years. After that time the Trial Steering Committee will consider requests from external parties for further analyses of the study data. The TSC will review the proposals and provide a view on scientific merit to the Sponsor and CI. Proposals that are scientifically well founded and have an academic basis and where relevant data

extractions and analyses are appropriately funded will not be refused. These will be considered as collaborative exercises where the contributions related to study design, conduct, database creation and maintenance and data analysis will be recognised in authorship of any scientific publication. The approach we will take will be to minimise any possibility of breach of participant confidentiality. Normally this will be achieved by minimising data travel. However, for the purposes of individual patient meta-analysis and other reasons, data may be transferred to other sites. Such transfer will require assurances on information security systems at the sites that data are to be transferred to and will involve a legal data transfer agreement. A log of all data requests and subsequent data transfers will be held at the Glasgow CTU.

## **13. DISSEMINATION POLICY**

### **13.1 Dissemination policy**

The data arising from this study will be owned by the University of Glasgow and NHS Greater Glasgow and Clyde.

Once the study has been completed, a final report will be prepared for publishing purposes, and to feedback research results to both sponsor and REC. This will be provided to sponsor/REC via email and will be made accessible to the wider research community on international study registry websites such as [clinicaltrials.gov](http://clinicaltrials.gov). The CI will have the right to publish the study data. There are no plans to notify participants of the outcome of the study. Participants will be provided with CI/PI contact details in the Patient Information Sheet. Participants will be advised upon requesting results that these will be made available once data analysis has been completed and/or the final study report has been compiled.

The main study documentation - study protocol and full study report – will be made accessible to the wider research community on international study registry websites such as [clinicaltrials.gov](http://clinicaltrials.gov) within 1 year of study opening.

### **13.2 Authorship eligibility guidelines and any intended use of professional writers**

Key contributors to the protocol and final report will be noted as authors, as will study clinicians who contribute significantly to the running/management of the study at site. All will be provided with a draft copy of the final report for review prior to publication. Criteria for individually named authors or group authorship will adhere to that of The International Committee of Medical Journal Editors.

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## 15. APPENDICES

### 15.1 Appendix 1 – Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.

## 15.2 Appendix 2. Demographic, medical and COVID-19 history

### Participant details

<b>CHI – Place Label</b>	Age ..... Years      Sex: Male / Female Height _____      Weight _____
Ethnicity	<input type="checkbox"/> Arab <input type="checkbox"/> Black <input type="checkbox"/> East Asian <input type="checkbox"/> South Asian <input type="checkbox"/> West Asian <input type="checkbox"/> Latin American <input type="checkbox"/> White
Date of admission	..... / ..... /
COVID-19 symptom onset date	... / ... /
Date of COVID-19 diagnosis	... / ... /
Blood pressure at presentation	Systolic / Diastolic (mmHg)
Heart rate at presentation	bpm
Initial troponin, ng/L	
Peak Troponin I, ng/L	
Date of peak troponin I	..... / ..... /
Initial point of care	A&E / AMRU / CCU / Medicine / Care of Elderly / Surgery / ICU
Second point of care	AMRU / CCU / Cardiology / Medicine / Care of Elderly / Surgery / ICU
Third point of care	AMRU / Cardiology / Medicine / Care of Elderly / Surgery / ICU
Date of discharge	..... / ..... /

### Co-morbidity

#### Charlson Comorbidity Index (CCI)

Predicts 10-year survival in patients with multiple comorbidities.

Age

<50 years

0

50–59 years

+1

60–69 years

+2  
70–79 years  
+3  
≥80 years  
+4

**Myocardial infarction**

History of definite or probable MI (ECG changes and/or enzyme changes)

No	0
Yes	+1

**CHF**

Exertional or paroxysmal nocturnal dyspnoea and has responded to digitalis, diuretics, or afterload reducing agents

No	0
Yes	+1

**Peripheral vascular disease**

Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)

No	0
Yes	+1

**CVA or TIA**

History of a cerebrovascular accident with minor or no residual and transient ischemic attacks

No	0
Yes	+1

**Dementia**

Chronic cognitive deficit

No	0
Yes	+1

**COPD**

No	0
Yes	+1

**Connective tissue disease**

No	0
Yes	+1

**Peptic ulcer disease**

Any history of treatment for ulcer disease or history of ulcer bleeding

No	0
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	Yes +1
Liver disease	
Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)	
<b>None</b> <b>0</b>	
Mild	+1
Moderate to severe	+3
Diabetes mellitus	
<b>None or diet-controlled</b> <b>0</b>	
Uncomplicated	+1
End-organ damage	+2
Hemiplegia	
	<b>No</b> <b>0</b>
	Yes +2
Moderate to severe CKD	
Severe = on dialysis, status post kidney transplant, uraemia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	
	<b>No</b> <b>0</b>
	Yes +2
Solid tumour	
<b>None</b> <b>0</b>	
Localized	+2
Metastatic	+6
Leukaemia	
	<b>No</b> <b>0</b>
	Yes +2
Lymphoma	
	<b>No</b> <b>0</b>
	Yes +2
AIDS	
	<b>No</b> <b>0</b>
	Yes

Is this a COVID-19 patient?

For research purposes only; answer does NOT impact results.

Confirmed positive

Suspected

Unlikely

Confirmed negative

**Outcome**

= CCI index (points)

= % estimated 10-year survival


<b>COVID Risk score</b>	
ISARIC-4 WHO	

<b>Cardiovascular symptoms</b>	
Angina	<u>Canadian</u> Cardiovascular Society angina class: 1 / 2 / 3 / 4
	If angina is reported, then subject to complete angina diary
Function s	New York Heart Association Functional Class 1 / 2 / 3 / 4

<b>CV Risk scores</b>	
Heart age score	<a href="https://www.bhf.org.uk/informationsupport/risk-factors/check-your-heart-age">https://www.bhf.org.uk/informationsupport/risk-factors/check-your-heart-age</a>
QRisk3 Risk score	<a href="https://www.qrisk.org/three/index.php">https://www.qrisk.org/three/index.php</a>

Smoking status, defined as per the internationally established definitions [https://www.cdc.gov/nchs/nhis/tobacco/tobacco\\_glossary.htm](https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm)

Current smoker:	An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes. Beginning in 1991 this group was divided into “every day” smokers or “some days” smokers.
Never smoker:	An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
Former smoker:	An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview
Some days smoker:	An adult who has smoked at least 100 cigarettes in his or her lifetime, who smokes now, but does not smoke every day. Previously called an “occasional smoker”.

Every day smoker:	An adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day. Previously called a “regular smoker”.
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**Pre-existing preventive cardiovascular therapy (medication prescribed prior to initial admission)**

Aspirin / Clopidogrel / Ticagrelor	ACE-I or ARB
Statin	Mineralocorticoid (spironolactone or eplerenone)
Beta-blocker	
Anticoagulation = warfarin or NOAC (circle)	

**Discharge preventive therapy (final discharge medication)**

Aspirin / Clopidogrel / Ticagrelor	ACE-I or ARB
Statin	Mineralocorticoid (spironolactone or eplerenone)
Beta-blocker	
Anticoagulation = warfarin or NOAC (circle)	


**COVID-19**

COVID-19 diagnosis		
Clinical diagnosis	Yes	No
Laboratory test - positive PCR test	Yes	No
Laboratory test – antibody test	Yes	No
Radiology diagnosis - CXR	Yes	No
CXR findings		
Radiology diagnosis – CT scan	Yes	No



CT findings		
C-19 = main/primary cause of admission to hospital i.e. suspected/known on admission (community acquired)	Yes	No
C-19 = developed in hospital (nosocomial)		
Admission diagnosis = non-COVID; i.e. COVID-19 diagnosed occurred in-hospital	Yes	No
Healthcare worker	Yes	No
ICU	Yes	No
COVID-19 treatment		
Supplemental oxygen		
Non-invasive respiratory support e.g. BIPAP, CPAP		
Invasive ventilation		
Extracorporeal membrane oxygenation		
Inotropes		
Haemodialysis		
COVID-19 Research Study: <u>TITLE</u> = .....		
Control – no treatment or placebo		
Antiviral – e.g. Remdesivir		
Antiviral (other) Lopinavir 400mg-Ritonavir 100mg or		
Immune regulator e.g. tocilizumab, sarilumab		
Steroid e.g. Dexamethasone		
Colchicine		
Aspirin		
Plasma		
Blinded study drug		
Other – please specify .....		

## Myocarditis Diagnostic Criteria

Caforio et al. Position statement of the ESC Working Group on Myocardial and Pericardial Diseases, European Heart Journal (2013) 34, 2636–2648 [68].

<b>Clinical presentations (A) (TICK if present)</b>	
	Acute chest pain, If yes circle / mark - pericarditic / pseudo-ischaemic (myocarditis) / ischaemic / dyspepsia / pleuritic.
	New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
	Subacute/chronic (.3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
	Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death Unexplained cardiogenic shock
	= TOTAL NUMBER PRESENT
<b>Diagnostic criteria (TICK if present)</b>	
	I. ECG/Holter/stress test features - Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
	II. Mycardiocytolysis markers – elevated troponin
	III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR) - New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavity thrombi
	IV. Tissue characterization by CMR – Modified Lake Louise Criteria (T2 map abnormality +/- T1 abnormality (native T1 map, late gadolinium enhancement, extracellular volume (ECV)
	= TOTAL NUMBER PRESENT

### Diagnostic criteria

Clinically suspected myocarditis if  $\geq 1$  clinical presentation and  $\geq 1$  diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis  $\geq 50\%$ ), if known; (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) Suspicion is higher with higher number of fulfilled criteria.

A - If the patient is asymptomatic  $\geq 2$  diagnostic criteria should be met.

**Myocarditis should be suspected in the presence of:**

1 or more of the clinical presentations, with or without ancillary features (see below),  
and

1 or more of the diagnostic criteria from different categories (I to IV) in Table 4 or when the patient is asymptomatic, 2 or more diagnostic criteria from different categories (I to IV).

To completed by clinician:

**ACS (at any time)**

Myocardial injury is defined as a high sensitivity troponin I > upper reference limit (99<sup>th</sup> centile).

Myocardial injury	Yes / No
Myocardial injury	Acute / chronic
ACS	Yes / No
Initial primary diagnosis	Type 1 MI / Type 2 MI / Type 3 MI / Myocardial Injury (Cardiac / Non-cardiac)*
Initial secondary diagnosis	Type 1 MI / Type 2 MI / Type 3 MI / Myocardial Injury (Cardiac / Non-cardiac)
Final primary diagnosis	Type 1 MI / Type 2 MI / Type 3 MI / Myocardial Injury (Cardiac / Non-cardiac)
Final secondary diagnosis	Type 1 MI / Type 2 MI / Type 3 MI / Myocardial Injury (Cardiac / Non-cardiac)

\*For T2MI / myocardial injury, circle either cardiac or non-cardiac

**T2MI / Myocardial Injury - Inciting cause or associated (tick all/multiple)**

CARDIAC	NON-CARDIAC
Tachyarrhythmia	Anaemia
Bradyarrhythmia	Hypoxia
Coronary embolus/spasm/dissection/microvascular	Renal disease
Heart failure / cardiomyopathy	Surgery (recent)
Hypotension	Pulmonary embolism
Hypertension	Infection – COVID-19
Structural heart disease e.g. valve	Infection – non-COVID: - Chest, Abdomen,

	UTI, Cellulitis, CNS, other - specify
Infection – endocarditis, myocarditis, pericarditis	COPD
Stress	
Other – specify	